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BLOOD-SUCKING VECTORS OF ENCEPHALITIS: EXPERIMENTAL TRANSMISSION OF ST. LOUIS ENCEPHALITIS* TO WHITE SWISS MICE BY THE AMERICAN DOG TICK, DERMACENTOR VARIABILIS SAY†

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SINCE the epidemic of acute encephalitis in the St. Louis area which occurred in the summer of 1933 and recurred in the summer of 1937, many investigators have been interested in this disease entity, and much experimental work has been done with the virus isolated from brain tissue of fatal cases in human beings. The mode of transmission of St. Louis encephalitis has been of special interest. While there are many opinions, the consensus has seemed to favor person-to-person transmission by droplet infection. Certain features of this disease, however, suggest the possibility of a blood-sucking vector: (1) The virus has never been isolated from nasopharyngeal washings. (2) there is only meager evidence to suggest case to case transmission. (3) the disease occurs in summer and early autumn. (4) during the 1933 epidemic the first cases were reported from St. Louis County in areas adjacent to wooded districts in the watershed of a small stream, the River Des Peres. Only later in the epidemic were cases reported in the city proper, and these cases were most numerous in precincts adjoining the county line. (5) That an endemic focus exists in the St. Louis area is indicated by the occurrence of two proved cases of St. Louis encephalitis during August, 1939, in Clayton, a suburb of St. Louis, and the occurrence of another proved case during June, 1940 in Glendale, also a suburb. It is pertinent to note that throughout the epidemic of 1933 there was a high per capita incidence of St. Louis encephalitis in these outlying communities, the second highest occurring in Glendale.

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*Hubbard strain.

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With these facts in mind we sought to demonstrate, first, whether a blood-sucking vector is capable of being infected by the virus of St. Louis encephalitis, and second, if so infected, whether the disease can be transmitted to susceptible animals by bite. A survey of the literature emphasized the importance of blood-sucking vectors in other virus encephalitides. Syverton and Berry[1-4] conducted extensive studies of the wood tick *Dermacentor andersoni* Stiles, demonstrating hereditary infection and experimental transmission of the western type of equine encephalomyelitis. Several genera of mosquitoes and assassin bugs are also thought to be involved in the epidemiology of western equine. Similarly a number of species of Ixodes have been implicated in Russian encephalitis; two genera of mosquitoes in Japanese B; the wood tick, the bedbug, and possibly a mosquito in lymphocytic choriomeningitis. House and stable flies studied in connection with the epidemiology of poliomyelitis have given positive results. Recent work by Hammon and Howitt and their associates[5-13] has shown the natural occurrence of the virus of St. Louis encephalitis in the mosquito *Culex tarsalis,* as well as the presence of antibodies in the blood of numerous species of mammals and birds.

The common dog tick *Dermacentor variabilis* was selected as the blood-sucking vector for the experimental work reported here. *Dermacentor variabilis* must be differentiated from *Dermacentor andersoni,* well known as the vector of Rocky Mountain spotted fever. While differentiation is often difficult on casual inspection, the two species may be distinguished readily on close examination of the spiracular plates under a binocular. The goblets composing the spiracular plate of *Dermacentor variabilis* are smaller and more numerous than those of *Dermacentor andersoni.*

The following is a brief summary of the life cycle of variabilis as we observed it in the laboratory: Adult females required on the average of from four to six days for complete engorgement. Four days after complete engorgement the first eggs appeared. Within fifteen days these hatched into larvae having six legs. The latter, if fed, metamorphosed ten days later into eight-legged nymphs. These nymphs in turn became adults (eight legs) in from six to eight days following engorgement. It is of importance to point out that a blood meal is required before metamorphosis from the larval to the nymphal stage and from the nymphal to the adult stage can occur. If such a blood meal is not available, the tick enters a diapause or latent stage. During diapause, which may extend for a long time, the tick survives without food, with a minimum of moisture, and often under extremely adverse conditions. This is also true for the egg. The life cycle of from forty-five to fifty days, observed in the laboratory under optimum conditions, may be extended in nature two years or longer. Certainly ticks can survive a winter in any stage of their development.

The primary phase of this experimental work concerned the question whether the tick *Dermacentor variabilis* could be infected by feeding on an animal previously inoculated with St. Louis encephalitis virus. Ticks in various stages of the life cycle, larvae, nymphs, adults, were allowed to feed on white Swiss mice or Syrian hamsters which had been inoculated with large doses of virus, usually intraperitoneally. Since the virus is present in the blood stream for a relatively short period, ticks were given opportunity for attachment as soon as possible after inoculation. When engorgement was satisfactory, the ticks were removed carefully and ground in an agate mortar with a small amount of broth. The resulting extract was inoculated intraperitoneally into young white Swiss mice 2 to 3 weeks of age. (This age group was chosen because it has been established that young mice are extremely susceptible to small doses of virus, even when injected intraperitoneally. Extracts of tick bodies obviously are not sterile bacterially. For this reason the intraperitoneal route of inoculation is of particular advantage in this work. In no instance were we able to demonstrate evidence of bacterial infection in animals so inoculated, and all cultures of the peritoneal sac and of organs, usually spleen and lung, were negative.) The young mice inoculated intraperitoneally with extracts of tick bodies were observed carefully. In from nine to thirteen days definite evidence of illness, often with convulsions, was noted. Brains removed from such animals were injected intracerebrally into normal controls, which developed typical symptoms of encephalitis in from three to four days. The virus which was recovered was readily identified as the St. Louis type by appropriate mouse and egg protection tests, using the serum of rabbits hyperimmunized against St. Louis encephalitis virus, Hubbard strain.

Having shown the dog tick capable of being infected by the virus, the next phase of the experiment was undertaken to determine whether encephalitis could be transmitted to other animals by the bite of such infected ticks. Accordingly, ticks in all stages of development were given an initial feeding on infected animals, after which they were transferred to normal white Swiss mice 2 to 3 weeks of age. Engorgement was continued on the second host. In from nine to fourteen days signs of illness, often convulsions, appeared. Here again, we were able to recover the virus from the second host, and in every instance the virus was identified as the St. Louis type. It is of interest that when older mice were used as the second host, signs of illness were seen, such as listlessness, lack of interest in food, hunched position, and ruffled fur. These older animals, however, recovered. Eight to twelve weeks later we were able to demonstrate the presence of a high titer of antibody against St. Louis encephalitis virus in the blood stream of some of these recovered mice. Others in this group showed a marked resistance to intracerebral inoculation of virus, withstanding as much as 10,000 minimal lethal doses.

Another phase of the experimental work concerned hereditary transmission of the virus. Adult female ticks were allowed to feed on an inoculated hamster. After complete engorgement, eggs were laid. In each case an extract of the eggs was injected intraperitoneally into young white Swiss mice. In from nine to fourteen days evidence of infection was apparent. The virus of St. Louis encephalitis was recovered from the brains of these young mice by intracerebral passage to older mice and was identified by protection tests in the usual manner. Likewise, larvae hatched from these eggs were studied for the presence of virus in their bodies. An extract prepared by grinding the larval bodies was inoculated into young mice. Definite signs of infection were noted within from nine to fifteen days. Further, larvae were allowed to attach themselves on young white Swiss mice, and in from nine to fifteen days signs of infection were noted. Similar results were obtained for the nymphal and adult stages of development. Adult female ticks raised in the laboratory from infected eggs were allowed to engorge on normal hamsters. The virus was recovered from an extract of their eggs. The above series shows that the St. Louis encephalitis virus can be transmitted from an infected female through her eggs, through all stages of subsequent development, and is present in the eggs of the second generation.*

Finally, we were interested in ascertaining for what period of time the virus can remain viable in the body of the tick. To date, we have found that the virus can be recovered regularly from the bodies of dormant ticks for at least four months after infection. Further experiments along this line are in progress.

In conclusion it may be said that the common dog tick *Dermacentor variabilis* is capable of being infected by feeding on inoculated animals and, once infected, can transmit the virus to normal susceptible animals by bite. Further, a female can transmit the infection to her offspring through the egg and through all stages of metamorphosis into the second generation. A tick once infected remains infected for at least four months. Thus far, the virus of St. Louis encephalitis has not been recovered from ticks collected in nature, but no extensive studies of this problem have been undertaken.

It is not our feeling that the dog tick is the natural vector responsible for the transmission of St. Louis encephalitis virus to man. No history of tick bite has been obtained in any case of St. Louis encephalitis observed. However, it is possible that the tick may play a role in the natural epidemiology of the disease by maintaining the virus as an endemic focus in lower animals, and that the virus may be carried to human beings by another blood-sucking vector such as the mosquito, possibly *Culex tarsalis,* as the work of Hammon suggests. The present

*Since the presentation of this report, virus has been shown to be present in the bodies of larvae hatched from second generation eggs. Such larvae are capable of transmitting the virus by bite to suspectible young mice.

work is of theoretical significance, since it represents the first successful transmission of the virus of St. Louis encephalitis to experimental animals by a blood-sucking vector. A preliminary account of this work was published in 1941.[14]

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EXPERIMENTAL INVESTIGATION OF MEASLES

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MEASLES is one of the most prevalent of human virus diseases, since some 97 per cent of people in civilized countries suffer from it at some time in their life. Yet, despite the fact that it is widespread and that prior to the use of sulfonamide drugs it caused a high mortality, particularly in young children, comparatively little work has been done with the agent or with the experimental disease in the laboratory.

The reason for this is simple. Despite many attempts, the virus has been successfully transmitted only to primates—particularly *Macaca mulatta*. Even in these it is a mild disease with evanescent signs and symptoms which tend to disappear on animal passage. In addition to this lack of a satisfactory experimental animal and partly on account of it, no serologic reaction has yet been developed with the virus comparable to those proving such useful tools in investigation of other virus diseases.

The many attempts which have been made to cultivate the virus of measles by one or other of the techniques used for other viruses have been reviewed elsewhere.[1] It will perhaps suffice to say that some authors have reported failures, while the claims to success of most of the others of cultivation on the membranes of the developing chick, in tissue culture, or in symbiosis with bacteria are open to doubt on one ground or another. In fact, up to 1938 only the results of Plotz,[2] with tissue, would seem to have been certainly successful.

Four years ago we began a study of the cultivation of this virus in the developing chick embryo and in tissue culture and have succeeded in growing it not only in tissue culture[3] and on the chorioallantois,[4, 5] but also in the amniotic and allantoic cavities. Most of the cultivation has been made by the Burnet technique on the chorioallantois. Of twenty-seven attempts to establish strains, seventeen have been successful and one of those has been propagated through 120 passages during more than seventeen months. It should be noted that cultivation has been possible in the absence of any regularly occurring lesions in the chick or its membranes. At first indeed, the only way of assuring ourselves that the strain was being successfully maintained was by inoculation of the egg material into monkeys. This produced characteristic measles, but the disease, never very severe, tended to become even milder with the use of material from later passages. It seems

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possible that failures reported by other investigators may be explained in part by this lack of any striking evidence of the presence of the virus either in the embryo or in the monkey.

Despite the lack of any such striking evidence, passage material which had been tested to exclude the presence of contaminating bacteria or other viruses was injected into children, originally in collaboration with Dr. Joseph Stokes, Jr., Dr. G. C. O'Neil, and Dr. E. P. Maris of the Department of Pediatrics of the University of Pennsylvania.[1, 6, 7] The very mildness of the disease produced in monkeys, indeed, led us to hope that the disease in children might be milder than that seen in nature; while the fact that monkeys which had developed measles from egg-passage virus were immune to challenge inoculations with infected human material[3, 5] suggested that the vaccination disease might produce a similar immunity in man.

TABLE I

RESULTS IN PHILADELPHIA PRIOR TO JUNE, 1942

ROUTE OF INOCULATION	TYPE OF DISEASE				
	MODERATE	MILD	MINIMAL	DOUBTFUL	NONE
Past History From Physicians					
Intranasal drip	5	4	2	16	3
Subc.				3	2
Intradermal	15	31	43	21	1
Inhalation spray	5	10	22	1	
	25 (14%)	45 (24%)	67 (36%)	41 (22%)	6 (3%)
Past History From Parents					
Intranasal drip		3	5	5	19
Subc.					4
Intradermal	2	5	18	4	2
Inhalation spray	2		2		
	4 (6%)	8 (11%)	25 (35%)	9 (13%)	25 (35%)

The expectations have been at least partially fulfilled. Measles has been produced in the majority of children by the use of egg-passage material which gave in the monkey only mild and transitory disease, and human inoculation has thus confirmed that the virus of measles was being successfully propagated and that the mild syndrome in the monkey was indeed measles. Furthermore, the disease in children has been in almost every instance milder than the mildest cases of the natural infection. I shall describe in more detail the disease in the children and then refer briefly to the evidence now accumulating on the protection afforded by the vaccination against natural infection or challenge inoculation.

Up to the end of June, 1942, 255 children, in twenty-seven groups, had been inoculated with egg-passage material in Philadelphia. It will be noted from the pooled results in Table I that the results have been broken down in several ways. The primary division depends upon the source of the negative history of previous measles which was obtained in every case. As might be expected, those children who had been fol-

lowed by physicians since birth gave a higher proportion of demonstrated disease—74 per cent with only 3 per cent negative—than did those in whom reliance had to be placed on the word of the parents—52 per cent positive and 35 per cent negative.

The results are also given in terms of route of inoculation. The administration by means of intranasal drip, which was used in earlier work, gave poor results—30 per cent positive and 36 per cent negative—compared with those following the later-adopted methods of intradermal inoculation, in which 80 per cent were positive, or inhalation of a finely divided spray, in which 98 per cent were positive.

The degree of reaction has also been indicated, and Table II shows the basis on which such division into moderate, mild, minimal, and doubtful has been made. In this earlier work, cases in which the children showed no Koplik spots were termed doubtful, even though morbilliform rash appeared at about the right time after inoculation. Of particular interest is the fact that even in the patients with the most severe cases cough was almost always absent and malaise was mild and transitory.

TABLE II

CLASSIFICATION OF REACTIONS

	MODERATE	MILD	MINIMAL	DOUBTFUL
Exanthem	Typical but rarely florid	Light	Light	Light
Enanthem	Present	Present	Present	None
Malaise	Mild	Slight or none	None	None
Cough	Rare	None	None	None
Nasopharyngitis	Moderate	Mild	Very mild	Very mild
Conjunctivitis	Present with photophobia	Present without photophobia	Slight	Slight
Temperature	102° F. or higher	100.8 to 101.8° F.	Under 100.8° F.	Under 100.8° F.

It was important to determine whether the mild vaccination disease would revert to the naturally severe type on passage to another child. Thirty-five presumably susceptible children were exposed to the inoculated groups. Of these, sixteen showed nothing, six gave a doubtful response, and thirteen showed a disease identical with that in the inoculated children. Of these thirteen, three had moderate, one mild, and nine minimal response. Thus one human passage did not change the character of the vaccination disease.

Since July 1, 1942, two other more extensive studies have been in progress under the auspices of the Commission on Measles and Mumps of the Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army. Tables III and IV show the results to date. In Baltimore, 827 colored children with negative history of measles derived from the parents have been vaccinated by Dr. Hodes and Dr. Gellis, and 412 of these have been carefully followed. Of these,

145 have shown definite signs of mild measles and it must be recognized that many light and transient rashes may well have been missed in these negro children.[8] In Philadelphia 199 susceptible white children, followed from birth by physicians, have been vaccinated by Dr. Stokes and Dr. Maris, and 172 of these have been carefully followed. In this case 131 have shown definite signs of mild measles. Both of these latter groups have shown a low incidence of Koplik spots, sixteen per cent and 25 per cent, respectively, due perhaps to further modification in the virus after prolonged passage in the chick embryo.

In all, a total of 1,281 children have been vaccinated without harm in any instance. Of these, 839 have been carefully followed and 450, or 54 per cent, have shown definite signs of modified disease.

TABLE III

BALTIMORE RESULTS

	9 TO 18 MO.	18 MO. TO 2 YR.	2 TO 3 YR.	3 TO 4 YR.	4 TO 5 YR.	5 TO 6 YR.
Children showing some signs of measles	48 of 103 (46%)	26 of 57 (45%)	31 of 93 (33%)	19 of 58 (33%)	18 of 49 (36%)	3 of 17 (18%)

Only 16 per cent of the 412 children inoculated and checked showed Koplik spots. All inoculations were by the intradermal route.

TABLE IV

LATER PHILADELPHIA RESULTS

	6 to 18 MO.	18 MO. TO 2 YR.	2 TO 3 YR.	3 TO 4 YR.	4 TO 5 YR.	5 YR. AND OVER
Children showing some signs of measles	61 of 79 (77%)	10 of 19 (53%)	14 of 18 (78%)	18 of 21 (89%)	7 of 7 (100%)	21 of 28 (75%)

Only 25 per cent of the 172 children inoculated and checked showed Koplik spots. All inoculations were by the intradermal route.

Only meager data are yet available on the protection produced by vaccination. Twenty-four children were given challenge inoculations with blood from active cases of measles which produced typical disease in control children and monkeys. This severe test of immunity produced measles in ten of the twenty-four. Twenty-two children have been intimately exposed to the natural disease of which four have developed measles, three have shown a mild syndrome of questionable nature, and fifteen have remained well. Of particular interest in the latter group was one school where seven vaccinated children remained free of measles despite repeated exposure. Seventy per cent of thirty-five unvaccinated children in this school developed the disease.[7]

SUMMARY

It has been possible to cultivate the virus of measles in the developing chick embryo. Such egg-passage material injected by appropriate

routes produced measles of mild character in 80 per cent of known susceptible children. There is evidence that this mild disease affords some protection against the natural infection and that it is not enhanced in virulence by at least one human passage.

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THE EARLY RADIOLOGIC RECOGNITION OF MITRAL VALVE DISEASE

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MITRAL valve disease can readily be diagnosed when the history and physical and roentgenologic findings all indicate the effects of impaired valvular and myocardial function. Frequently, however, difficulty arises in establishing a definite diagnosis in children who present an equivocal history and ill-defined or transitory physical and roentgenologic changes. This paper will deal with early roentgenologic diagnosis of rheumatic mitral valve disease.

Identification of cardiac enlargement as soon as possible is a cardinal point in diagnosis because it may lead to a definite opinion when other data are unconvincing. In order to help decide which roentgenologic procedure is most helpful in diagnosing early mitral valve changes, twenty-five selected children were examined fluoroscopically and by means of teleroentgenograms and oblique views of the heart. Clinically the patients were diagnosed as having mitral insufficiency, mitral stenosis, and insufficiency or functional heart murmurs.

The teleroentgenograms were studied for alterations in the heart silhouette, and measurements were made to determine the heart rectangle: lung rectangle ratio described by Newcomer and Newcomer[1] and recommended by Ungerleider and Gubner for hospital use where data about patients' heights and weights are not available.[2] When the latter were available, the predicted transverse diameter of the heart was determined and compared with the actual transverse diameter according to the chart of Ungerleider and Clark,[3] and the same procedure was followed for the cardiac surface areas according to the nomogram of Ungerleider and Gubner.[4] Inasmuch as the chart starts with a patient's height of 5 feet and weight of 83 pounds, and the nomogram with 57 inches and 95 pounds, these determinations can be applied only to the older children. Eight were so examined.

The cardiothoracic ratios were also determined but were not included in the table, inasmuch as our findings agree with those of Seham, Shapiro, and Hilbert, who found this determination of little value.[5] The relationship of the apex of the heart to the midclavicular line was determined and found to be of little assistance.

OBSERVATIONS

Eleven boys and fourteen girls between 3½ and 14 years old were studied. Sixteen had a definite history of rheumatic fever, two were

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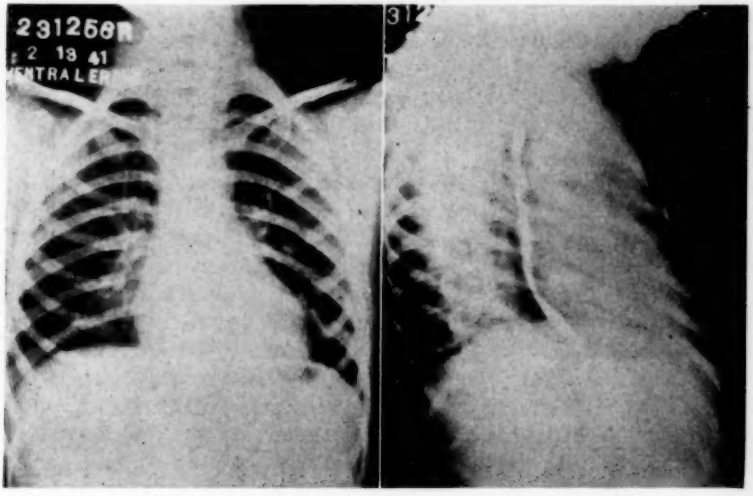
doubtful, and seven had no known rheumatic infection. Eight patients had definite systolic and diastolic murmurs at the apex. Seventeen had systolic apical murmurs which varied in intensity from a loud blowing systolic murmur to a faint apical whiff. On occasions no murmurs at all were heard in three of the patients, and three others had murmurs which varied considerably in intensity from time to time. Four patients were observed clinically for more than a year, nine were followed between two and three years, and four were followed up to six years. The remaining eight were seen for less than one year. The x-ray examinations were usually made at the beginning of the period of observation, and only the initial studies were recorded except for four patients in whom subsequent roentgenograms were of interest.



A. *B.*

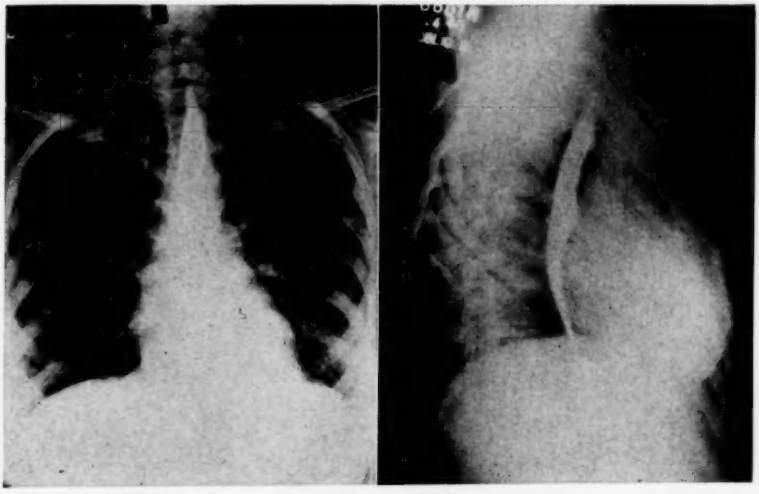
Fig. 1 (Case 1).—*A*, P. M., male, 4 years of age. No definite history of rheumatic fever was elicited, but the patient had had frequent upper respiratory infections. Examination at the time the films were taken showed a systolic blow at the apex, interpreted as a functional murmur. Several months later systolic and diastolic murmurs appeared at the apex, and the diagnosis was changed to mitral valve disease. Six months thereafter the apical murmurs changed again, only a soft apical blow being heard. The diagnosis was again altered to functional heart murmur. Two years after the first examination, double mitral murmurs reappeared and the diagnosis of mitral disease was considered definite. The teleroentgenogram was taken at the first examination. Although the cardiac contour is normal, the heart rectangle: lung rectangle ratio is 30 per cent, somewhat above normal.

B, Right anterior oblique projection with esophagus outlined with barium paste. The posterior indentation of the enlarged left auricle is well portrayed.

A diagnosis of mitral stenosis and insufficiency was made in the eight children with double apical murmurs. In five others the mitral systolic murmurs were considered indicative of mitral insufficiency, and in four there was disagreement as to whether the murmur was organic or not. It was not uncommon to see a diagnosis of a functional murmur at one examination altered to mitral insufficiency soon thereafter by another examiner and vice versa. Eight were considered as having definitely

functional murmurs. None of the children had heart failure. Four were unaware of a cardiac condition and had been referred for further study from their schools.

Electrocardiograms were available in twenty-three patients. No changes in axis deviation, P waves, or auriculoventricular conduction times were present except in two patients who had had an increased P-R interval during acute exacerbations.



A. *B.*

Fig. 2 (Case 19).—*A*, L. B., female, 13 years of age. There was a history of chorea and migratory joint pains. At the first examination a systolic apical murmur transmitted to the axilla was heard and interpreted as due to mitral insufficiency. Heart measurements from the teleroentgenogram taken then were normal, but cardiac fluoroscopy revealed an enlarged left auricle. Three years later systolic and diastolic apical murmurs were present and were unchanged five years after her first examination. The teleroentgenogram was taken at the second examination. The heart silhouette is normal and is not enlarged according to measurements.

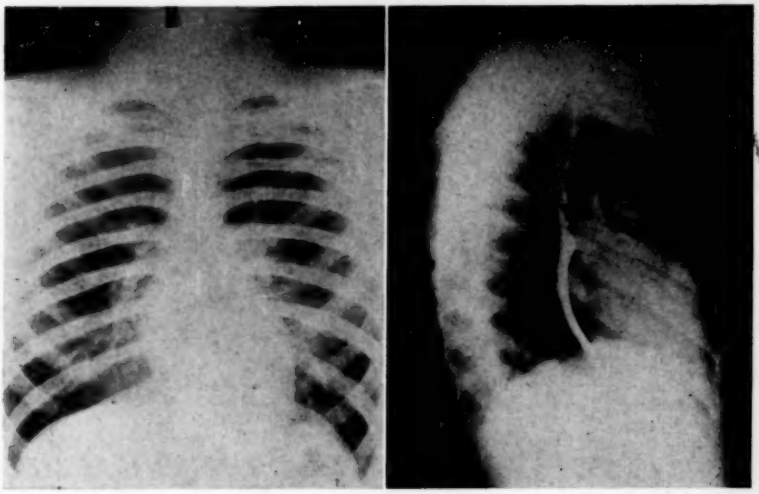
B, Right anterior oblique projection showing indentation of enlarged left auricle into barium-filled esophagus.

The teleroentgenograms revealed an apparently normal heart silhouette in twenty patients. Doubt existed whether or not the prominence in the region of the second left cardiac arc was indicative of pulmonary artery or conus enlargement in the other five. The films were reviewed with several pediatricians as well as roentgenologists, and the average score was sixteen films normal and the remainder doubtful or indicative of cardiac enlargement.

Routine fluoroscopic examination of the heart included inspection of the barium-filled esophagus. There was slight but definite posterior enlargement of the left auricle in all the patients as shown by indentation into the esophagus with the patient in the right anterior oblique projection. The usual angle in which the indentation was best portrayed varied from 55 to 80 degrees. This was determined fluoroscopically

before the oblique roentgenograms were made. No change in the course of the esophagus was noted in the posteroanterior projection. The left main bronchus likewise was in its normal position in all patients. In none did the left auricle approach the right heart border. In five patients there was anterior prominence of the right ventricle indicative of early outflow tract enlargement.

No definite evidence of left ventricular enlargement was seen. Although no definite determinations of the angle of clearance of the left ventricle from the thoracic spine in the left anterior oblique projection were made,[6] the left ventricle could readily be separated from the



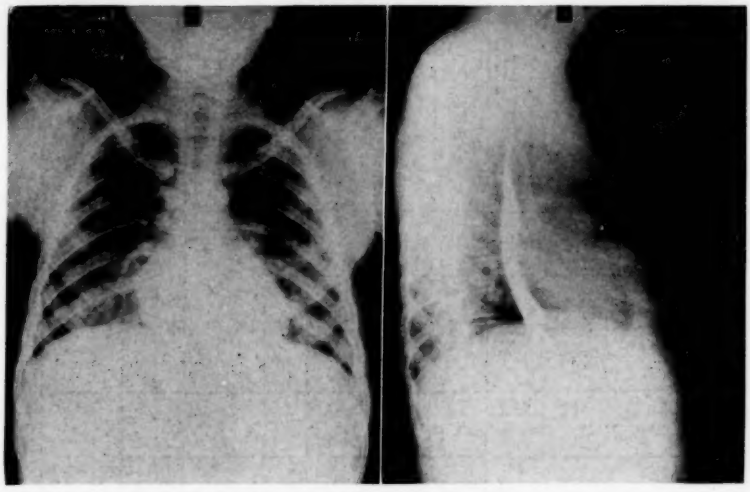
A. *B.*

Fig. 3 (Case 22).—*A*, B. M., male, 14 years of age. There was a definite history of rheumatic fever. A loud rough apical systolic murmur transmitted to the axilla was diagnosed as mitral insufficiency at the first examination. The teleroentgenogram taken then showed no evidence of heart enlargement, but fluoroscopy revealed an enlarged left auricle. Two years later the murmur was faint, and the examiner was unable to establish the presence of heart disease on the basis of his findings. The teleroentgenogram above was taken at this time. The heart contour is normal, and there is no evidence of enlargement.

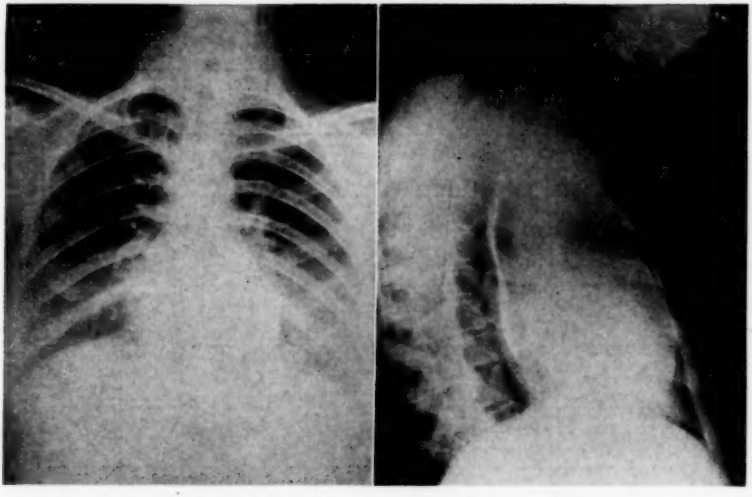
B, Right anterior oblique projection showing indentation of enlarged left auricle into barium-filled esophagus.

spine. The inferior interventricular notch could be identified above the diaphragm in all the patients, a finding usually indicative of a normal left ventricle. No definite enlargement of the right auricle could be seen. The pulsations of the great vessels were within normal limits, and no definite increase in the amplitude of pulsations of the hilar branches of the pulmonary arteries was present.

It was noteworthy that no definite pattern could be evolved in so far as the known duration of these patients' illnesses was concerned, nor were the murmurs more characteristic of mitral valve disease associated with more marked left auricular enlargement in this group.



A. *B.*



C. *D.*

Fig. 4 (Case 17).—*A*, M. L., female, 12 years of age. The patient was known to have a heart murmur since the age of 6 years. When 12 years old, a systolic apical murmur interpreted as functional was heard. The teleroentgenogram above was taken at that time and shows a normal heart according to measurements.

B, Right anterior oblique projection shows definite left auricular enlargement.

C, The patient was again seen at the age of 15 years. The teleroentgenogram shows no cardiac enlargement or distortion, and all measurements are within average limits.

D, Right anterior oblique projection showing a decrease in the degree of left auricular enlargement (compare with *B*).

TABLE I

CASE	AGE (YR.)	SEX	HISTORY OF RHEUMATIC FEVER	SYSTOLIC AND DIASTOLIC MURMURS	SYSTOLIC MURMUR	VARIABLE MURMURS	CLINICAL DIAGNOSIS	PREDICTED TRANSVERSE DIAMETER (MM.)	ACTUAL TRANSVERSE DIAMETER (MM.)	PREDICTED SURFACE AREA (SQ. CM.)	ACTUAL SURFACE AREA (SQ. CM.)	NORMAL HEART/LUNG (%)	ACTUAL HEART/LUNG (%)	HEART FAILURE	FOLLOW-UP
1	4	F	Pos.	×	×		M.S. and M.I.					26	30	0	Followed two years; developed double mitral murmur again after an interval in which only a systolic was heard
2	4	M	None		×		Funct.					26	30	0	Followed five years; murmur variable; none heard at last examination.
3	5	F	?		×		Funct.					26	26	0	Followed one year; systolic murmur unchanged
4	6	F	Pos.		×	×	M.I. ?					23	23	0	Followed one and one-half years; systolic murmur varied in intensity
5	7	M	Pos.	×			M.S. and M.I.					26	29	0	Followed six years; developed full-blown M. S., M.I., and A.I.
6	7	F	Pos.		×	×	M.I. ?					23	23	0	Seen with active rheumatic fever; murmurs variable; following one year

7	9	M	None		×		M.I. ?					26	28	0	No known heart disease; found at school examination
8	9	M	Pos.	×			M.S. and M.I.					26	24	0	Followed two and one-half years; systolic murmur persists
9	10	F	Pos.		×		Funct.	117	119	96	100	24	23	0	No follow-up
10	10	F	Pos.	×			M.S. and M.I.					26	25	0	No follow-up
11	11	F	Pos.		×		Funct.					26	24	0	Followed two years; systolic murmur persists
12	11	M	Pos.		×	×	M.I.	111	113	95	100	26	27	0	Repeated attacks of rheumatic fever; no definite murmurs; followed two years
13	12	M	Pos.		×		M.I.					26	28 5/9/42 46 12/7/42 30 12/29/42	0	Acute rheumatic fever; cardiac dilatation and recession; followed one year; no recurrence
14	12	M	?		×		M.I. ?					23	26 5/16/39 22 10/30/41	0	Followed three years; systolic persists; last diagnosis was "functional murmur"
15	12	F	None	×			M.S. and M.I.					26	27	0	Referred from school; unaware of heart disease
16	12	F	Pos.		×		Funct.					26	28	0	Followed one year; no change
17	12	F	None		×	×	Funct.	121	108	104	93	26	25	0	Followed three years; murmur variable and diagnoses changed

M.S., Mitral stenosis.
M.I., Mitral insufficiency.

TABLE I—CONT'D

CASE	AGE (YR.)	SEX	HISTORY OF RHEUMATIC FEVER	SYSTOLIC AND DIASTOLIC MURMURS	SYSTOLIC MURMUR	VARIABLE MURMURS	CLINICAL DIAGNOSIS	PREDICTED TRANSVERSE DIAMETER (MM.)	ACTUAL TRANSVERSE DIAMETER (MM.)	PREDICTED SURFACE AREA (SQ. CM.)	ACTUAL SURFACE AREA (SQ. CM.)	NORMAL HEART/LUNG RECTANGLE (%)	ACTUAL HEART/LUNG RECTANGLE (%)	HEART FAILURE	FOLLOW-UP
	12	M	Pos.		×		M.I.	116	115	101	100	26	27	0	Followed six months; no change
19 18	13	F	Pos.	×		×	M.S. and M.I.	121 125	118 108	101 108	105 6/14/37 104 10/24/30	26	26 24	0	Followed five years; first had a systolic murmur only; then double murmur
20	13	F	None		×		M.I.	108	110	99	102	23	23	0	Diagnosed at school examination
21	13	F	Pos.	×			M.S. and M.I.	148 106	140 110	126 118	112 6/14/37 128 6/20/40	26	33 30	0	Followed five years; murmurs persist unchanged
22	14	M	Pos.	×		×	Funct.	122 127	123 120	112 118	126 6/20/40 118 9/3/42	23	24 22	0	Followed two years; murmur at first rough and loud, gradually became less intense
23	14	F	Pos.		×		M.S. and M.I.					26	30	0	Followed six months; diastolic murmur appeared
24	14	M	None		×		M.I.					26	29	0	Followed two years; aortic lesion found
25	14	F	None		×		Funct.					23	23	0	Found at school examination; no heart disease suspected

A.I., Aortic insufficiency.

The heart rectangle:lung rectangle ratio was above normal in twelve patients and within normal limits in the remaining thirteen. A question as to the applicability of this procedure to children might arise because the normals determined by Newcomer and Newcomer apparently were based on patients examined in insurance and office practice, presumably adults. They emphasize their observation that the normal ratio varies with the type of cardiac configuration. Ungerleider and Gubner assert that the heart is considered enlarged if the ratio exceeds 28 per cent. It is conceivable that in youngsters the higher ratio might fall within average limits because the heart often assumes a more transverse position.

There were eight patients who could be checked with the chart and nomogram of Ungerleider and Clark and Ungerleider and Gubner. One was 10 years old, two were 11, two were 12, and three were 13 years old. One patient was 14 years old. In each the actual transverse diameter and cardiac surface area was the same or less than the predicted value, an observation which might lead to the assumption that the heart was not enlarged.

The relationship of the apex of the heart to the midclavicular line was normal in twenty patients. It could not be determined accurately in the remaining five because the patients' arms were held above their heads when the exposures were made, thereby distorting the clavicular shadows.

One patient developed subacute bacterial endocarditis and died two years after his last examination. The diagnosis of mitral valve disease was confirmed at autopsy.

DISCUSSION

These findings are in accord with the findings of those who reported that the first significant chamber enlargement to occur with mitral valve disease is left auricular enlargement.[7]

A word as to the anatomico-radiologic appearance of the left auricle would be in place here. The left auricle is a completely posterior chamber and does not enter into the formation of the heart silhouette as a rule. Sometimes the left auricular appendage may be elongated, particularly in long, narrow hearts, and it then appears on the left heart border between the inferolateral aspect of the pulmonary artery or conus and the upper angle of the left ventricle adjacent to the point of opposite pulsations. This site can be determined readily fluoroscopically. Sometimes the feeble pulsations of the auricular appendage itself can be observed fluoroscopically. The appendage is a thick muscular structure with little blood-containing capacity and is unimportant functionally. Its appearance on the left heart border is of little clinical significance and for practical purposes may be disregarded.

The esophagus is closely apposed to the posterior aspect of the left auricle. It passes anterior to the descending thoracic aorta, gradually

shifting from right to left in the posteroanterior projection and slightly forward in the lateral and oblique projections. Two gradually merging indentations may be seen on its anteromesial surface at the level of the transverse thoracic aorta and the left main bronchus. Beneath this site it is in close relationship to the left auricle, and early left auricular enlargement results in a third indentation which is best seen in the right anterior oblique projection and rarely in the posteroanterior position.

The other criteria mentioned for enlargement of the left auricle include elevation of the left main bronchus, widening of the angle of bifurcation of the trachea, narrowing of the left main bronchus, or the appearance of the left atrial border on the right cardiac border. None of these changes were observed in this group of patients.

SUMMARY

The earliest enlargement of the heart due to mitral valve disease is left auricular enlargement. This can best be diagnosed fluoroscopically by examining the patient in the right anterior oblique projection after administering a barium bolus. Even a slight degree of posterior deviation of the esophagus is significant and may occur long before the cardiac outline is otherwise altered.

Other methods for determining cardiac enlargement based on calculations made from teleroentgenograms and tables of the patients' heights and weights were found to be unreliable in detecting early left auricular enlargement. The frontal silhouette of the heart may retain a normal appearance even when the left auricle is considerably enlarged posteriorly.

It is necessary to examine patients with systolic apical or transitory murmurs with these facts in mind. A diagnosis of a functional murmur should not be made if there is roentgenologic evidence of an enlarged left auricle. Neither should a heart be considered normal if the murmurs are transitory or temporarily absent in the presence of an enlarged left auricle.

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THE EFFECT OF ILLNESS AND OTHER FACTORS ON THE APPEARANCE PATTERN OF SKELETAL EPIPHYSES

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THE epiphyses of the long bones and the nuclei of the tarsal and carpal bones follow to a greater or lesser degree a general pattern in the sequence of their appearance. For example, the nucleus of the capitate normally appears before that of the hamate, and both appear considerably before the epiphyses of the metacarpals and phalanges. It is customary, when presenting tables of time of appearance of the various ossification centers, to provide for each center a tolerance, or normal range during which it may appear. A child whose epiphyseal appearance is slow in comparison to the average may have the bulk of his bony nuclei appearing at the upper limit of this normal range. Conversely, a child with advanced skeletal growth will have most of his centers appearing in the lower part of the normal range for each center. In each child, however, the roentgenologist will observe some centers which, in time of appearance, do not conform to the general appearance pattern for that child. One center may be present in advance of several centers which are normally present first. Or one or more centers may be markedly delayed in their appearance, although centers which usually appear much later than they are well established. These aberrances in patterns of ossification are so common and of such proportions as to cause confusion in the appraisal of the skeletal age of a child. The cause of such disruption has been the subject of considerable controversy. The investigations presented here were undertaken in an attempt to reveal, if possible, some of the factors which may influence the development of ossification patterns.

Kohler[1] calls attention to such individual differences in ossification sequence and believes them to be familial. He states that when a given center is delayed in its appearance in relation to other centers in the child—in other words, is "displaced" in terms of time—one will be likely to find the same epiphysis delayed in other members of the same family. Buschke[2] emphasizes the importance of the genetic factor in his study of monozygotic twins. Pryor[3, 4] states unequivocably that ossification pattern is a genetic factor. Todd[5] and Francis,[6, 7] expressing Todd's theories, believe that the principal cause of such temporal "displacement" or misalignment of an epiphysis is the result of illness suffered by the child slightly before the epiphysis was to calcify. They believe that the systemic effect of such an illness depresses the calcification process and delays it for some time. Since such delay is assumed

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to affect only those centers whose cartilage is already undergoing proliferation in anticipation of calcification, other centers not yet that far along are unaffected and their calcification occurs on schedule. A center delayed by illness is, according to them, delayed not simply for the duration of the illness but for some time after with the result that a rather marked alteration in order results. Neither Todd nor Francis have to our knowledge published any evidence in support of their statements. Buschke and Pryor offer the likeness of patterns of monozygotic twins and triplets as evidence for the genetic factor. The likenesses of the ossification patterns of uniovular twins are real evidence of this genetic factor, but it does not disprove the illness theory as an added factor. Both theories may be correct.

Our series of skeletal x-rays on 175 children, covering all of the joints of the left side of the body (and part of the right side), which were taken at regular intervals from birth on, has given us an opportunity to investigate aberrant ossification and the factors which influence it. From our group of 175 children we have selected on the basis of completeness of x-ray series eighty-four whose data constitute the material for this study. Of these forty-seven are girls, and thirty-seven are boys. There are among them twenty-two pairs of nontwin siblings and three pairs of monozygotic twins. With few exceptions an entire series of x-rays of the hand, wrist, elbow, shoulder, hip, knee, ankle, and foot at birth, 1 month, 3 months, 6 months, 9 months, and 12 months of age and at six-month intervals thereafter until ossification is complete are available for each child. The time of appearance of each center may, of course, be accurately determined as falling between the date of the picture in which it first appears and the last previous picture. Such a procedure locates the date of appearance within three or six months, according to whether the picture was taken at a three- or six-month interval. We have attempted to refine these figures somewhat by estimating from the series of x-rays dealing with each center at what point calcification did begin.[8] With a bit of experience such judgment is not difficult. For example, if the capitate and hamate are absent in a child's 1-month-old picture, and both are present in the 3-month-old x-ray, it is obvious that they appeared between the first and third month. If the capitate is well formed and approximately circular, while the hamate appears as a tiny irregular white dot, it is probable that the capitate is the older of the two and that the hamate has only just begun to calcify. Further study of the rates of progress of the calcification as shown in the next picture and as demonstrated in the x-rays of other children makes it possible to estimate the actual age of appearance usually within two or three weeks during the first year and within six weeks thereafter. The accuracy of our estimates has been verified on children whom we have x-rayed at much more frequent intervals.

TABLE I

AGE AND ORDER OF APPEARANCE OF THE THIRTY-EIGHT OSSIFICATION CENTERS*

ORDER OF APPEARANCE	BOYS		GIRLS	
	MEAN AGE (MO.)	STANDARD DEVIATION (MO.)	MEAN AGE (MO.)	STANDARD DEVIATION (MO.)
Cuboid	.5	.7	.4	.8
Head of humerus	.7	.8	.9	.8
Capitate	2.4	1.8	2.3	2.1
Distal tibia	3.9	1.5	3.4	1.4
Head of femur	4.4	2.0	3.7	1.6
Lateral cuneiform	4.4	4.3	3.8	4.4
Capitulum	6.3	4.3	4.1	3.6
Greater tuberosity humerus	11.4	7.2	6.6	3.3
Distal fibula	12.5	4.1	9.3	2.6
Distal radius	13.0	4.7	10.8	4.4
Proximal third finger	16.2	5.3	10.4	3.1
Distal first toe	16.8	5.6	10.6	2.8
Distal first finger	18.4	6.2	12.8	5.0
Proximal third toe	19.5	5.2	12.2	3.8
Metacarpal, third	21.1	6.4	14.2	4.0
Medial cuneiform	21.9	9.9	16.7	8.5
Middle third finger	24.9	7.6	15.9	4.9
Triquetral	27.3	15.9	23.6	13.7
Metatarsal, first	27.7	4.7	20.1	3.3
Distal third finger	27.8	6.4	20.2	3.9
Middle cuneiform	28.4	11.2	21.3	7.6
Metacarpal, first	29.8	7.3	20.3	5.3
Proximal first toe	29.9	5.8	20.3	5.5
Navicular (foot)	33.4	13.5	25.8	11.1
Proximal first finger	34.8	7.9	21.6	5.1
Metatarsal, third	41.5	7.9	29.1	6.4
Greater trochanter femur	42.6	7.6	29.8	6.4
Lunate	46.0	19.3	34.6	14.2
Proximal fibula	47.0	11.8	32.6	9.3
Patella	51.9	11.6	34.8	8.5
Distal third toe	53.5	11.2	32.8	7.7
Navicular (hand)	60.1	14.1	47.8	12.3
Proximal radius	63.5	17.2	47.5	12.1
Greater multangular	64.3	19.7	47.0	14.8
Lesser multangular	64.4	15.2	48.3	14.8
Medial epicondyle humerus	73.6	17.5	41.3	9.9
Distal ulna	82.4	10.6	63.2	15.3
Epiphysis calcaneus	89.6	14.0	63.7	11.8

*From Pyle and Sontag.

The selection of the centers to be included in the study was somewhat arbitrary. The general basis, however, was that of securing an adequate representation of various areas of the body and types of centers and of securing a satisfactory age distribution. Since the metatarsals and tarsal phalanges and the metacarpals and carpal phalanges tend to appear somewhat as groups, and since they are rather heavily represented in numbers, we have used (of these groups) only the epiphyses of the third and first fingers and toes. The complete list is presented in Table I, together with standard deviations from Pyle and Sontag.[8]

METHOD OF COMPARISON

To create a standard of time of appearance of centers, it was necessary first to determine the time of appearance of each center in a group

of fifty boys and fifty girls.[8] The mean time of appearance of each center was then calculated for the two groups. These two series of means then served as a basis for the appraisal of the "earliness" or "lateness" of the appearance of each of the thirty-eight centers of each child. Boys were, of course, compared with the boys' standard and girls with the girls' standard. There is a slight difference in the order for the boys and girls.

The appearance of a center a month slow or a month fast differs greatly in significance according to the age of the child. A center which is one month slow in appearing when the child is 2 months old may be significantly slow, while a center one month slow at 8 years of age could be considered practically on time. To eliminate this age factor, we converted the time of appearance of each center into standard scores or Z scores, the formula for which is:

$$\frac{\text{Age of appearance} - \text{Group mean age of appearance of center}}{\text{Standard deviation}} = \text{Standard score.}$$

Thus any boy whose navicular appears at 60 months, which happens to be the mean for the group, would have a standard score of O. If it appeared at 70 months, it would have a score as follows:

$$\frac{70 - 60}{14.09} = +.71.$$

The plus sign of the score indicates that the center was slow in appearing.

By assigning a number to each center and plotting the standard score of its appearance time, it is possible to observe at once the entire epiphyseal growth pattern of the thirty-eight centers of a child and to compare such a pattern with that of others (see Figs. 1 to 12).

In addition to the standard score of each center plotted in relation to the group mean, the means of the standard scores for each year are plotted. For example, suppose that in child A seven centers appeared during the first year. The mean would be the sum of the scores of those seven centers divided by seven. Each yearly mean is computed in a like manner and is indicated in the figures by a heavy black dot (see Figs. 1 to 12). It is thus possible to see on one figure the time of appearance of any of the thirty-eight centers, both in relation to the group mean (0 standard score) and in relation to the mean of centers which appeared during the same year. The pattern of the yearly means shows the rate of growth of the child for each year as measured by time of appearance of centers. If a child's thirty-eight centers appeared in exactly the mean order of the group, all thirty-eight numbers on his plot would be approximately in a straight line. If his rate of appearance of new centers was the same as that of the mean for the group, his straight line of thirty-eight numbers would fall exactly on the zero line or mean of the standard score. The dispersion of numbers on the plot indicates then the degree to which this child differed from the group mean in the order in which his centers appeared. The

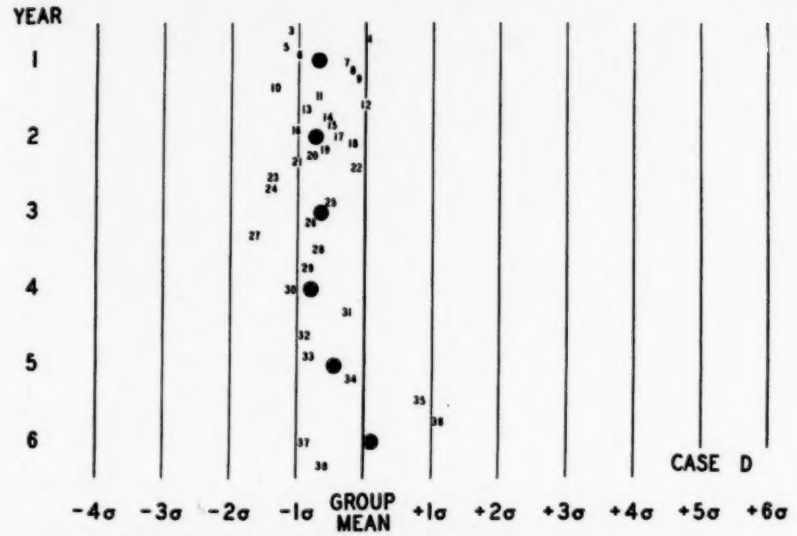


Fig. 1.—Diagram of the distribution of standard scores of the time of appearance of thirty-eight ossification centers in child D. Each number represents a specific center and the black dots represent Z score means of centers appearing during each of the six years.

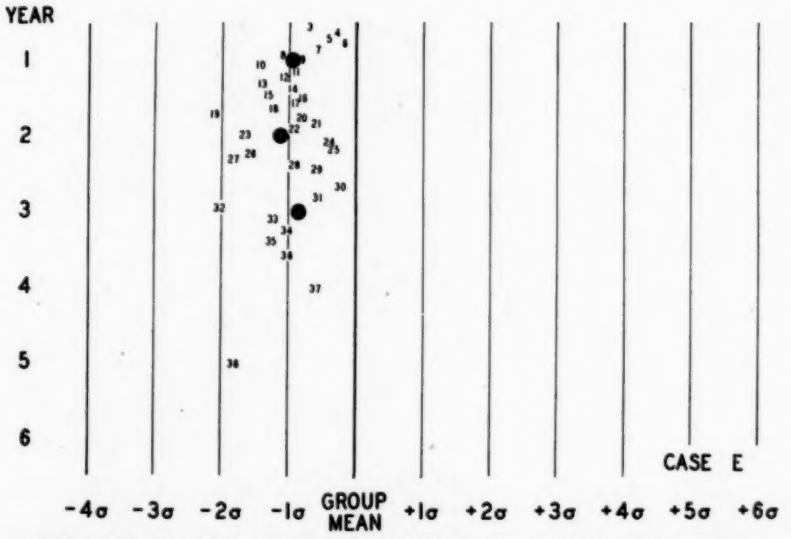


Fig. 2.—Diagram of the distribution of standard scores of the time of appearance of thirty-eight ossification centers in child E. Each number represents a specific center and the black dots represent Z score means of centers appearing during each of the three years.

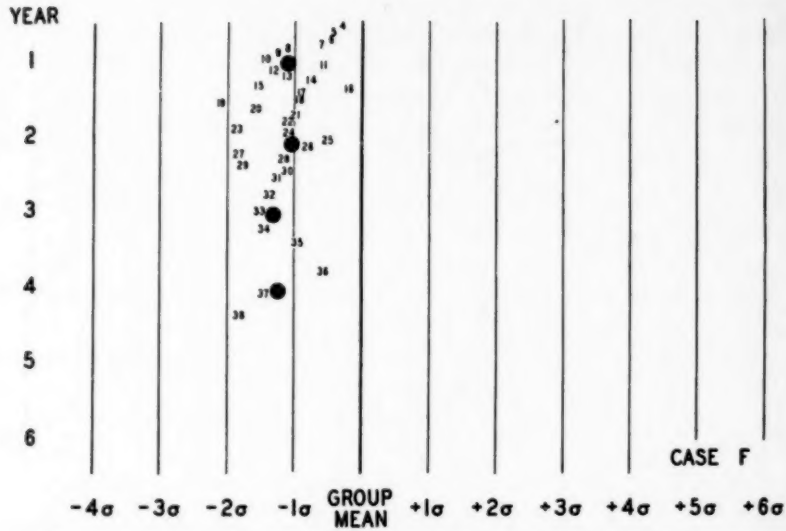
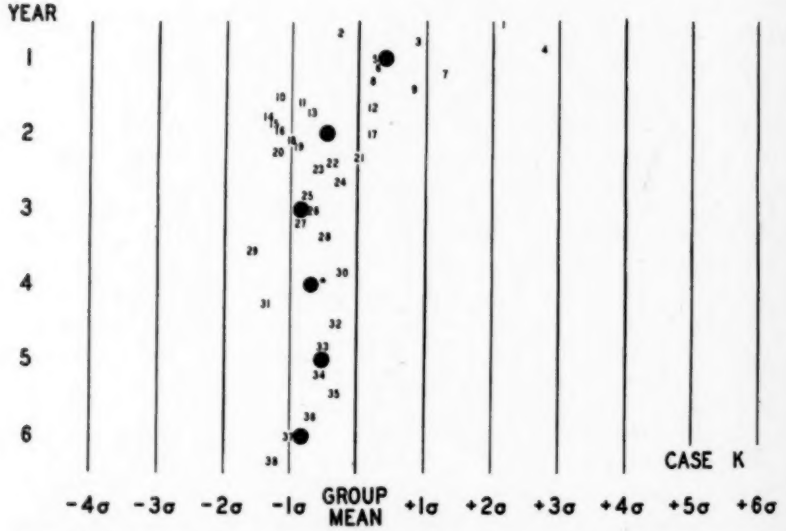


Fig. 3.—Diagram of the distribution of standard scores of the time of appearance of thirty-eight ossification centers in child F. Each number represents a specific center and the black dots represent Z score means of centers appearing during each of the four years.



*Interpolated mean.

Fig. 4.—Diagram of the distribution of standard scores of the time of appearance of thirty-eight ossification centers in child K. Each number represents a specific center and the black dots represent Z score means of centers appearing during each of the six years.

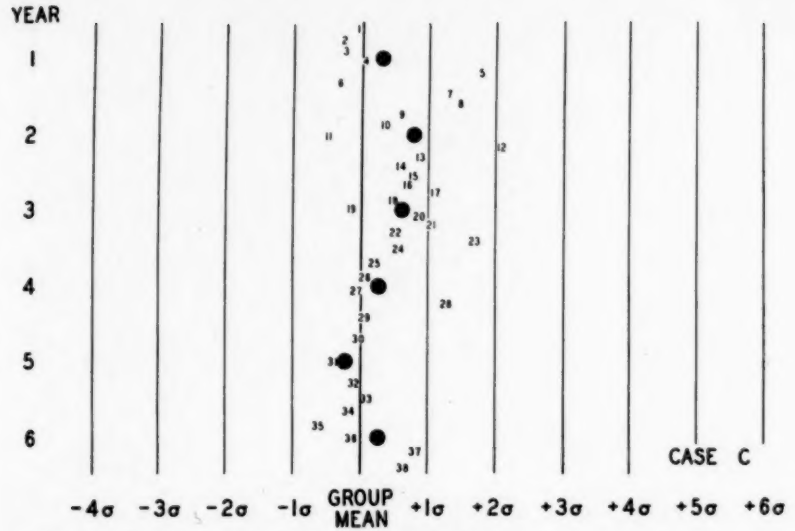


Fig. 5.—Diagram of the distribution of standard scores of the time of appearance of thirty-eight ossification centers in child C. Each number represents a specific center and the black dots represent Z score means of centers appearing during each of the six years.

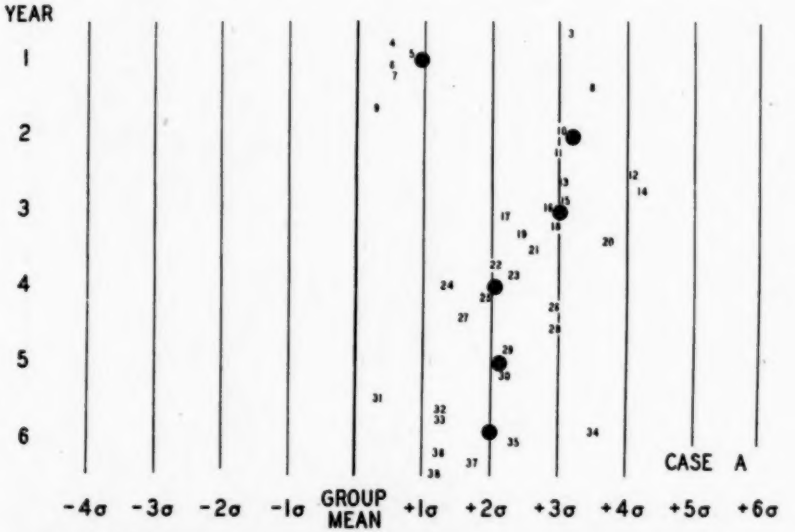
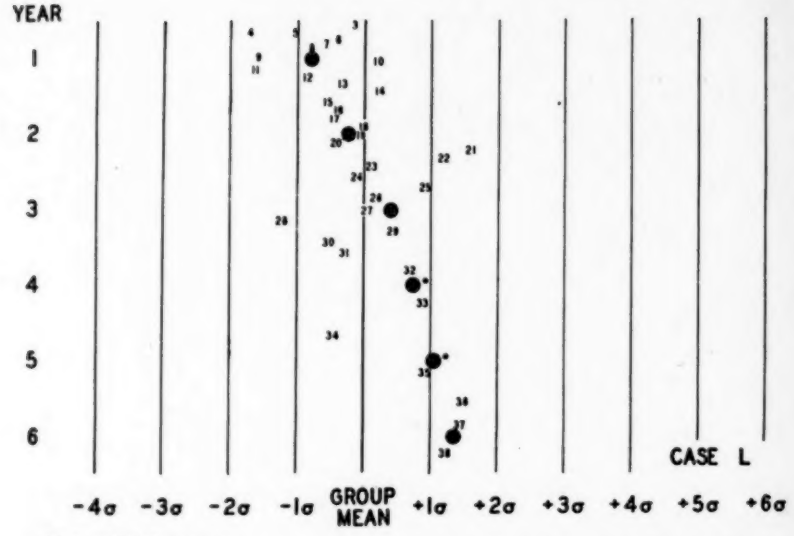


Fig. 6.—Diagram of the distribution of standard scores of the time of appearance of thirty-eight ossification centers in child A. Each number represents a specific center and the black dots represent Z score means of centers appearing during each of the six years.



*Interpolated means.

Fig. 7.—Diagram of the distribution of standard scores of the time of appearance of thirty-eight ossification centers in child L. Each number represents a specific center and the black dots represent Z score means of centers appearing during each of the six years.

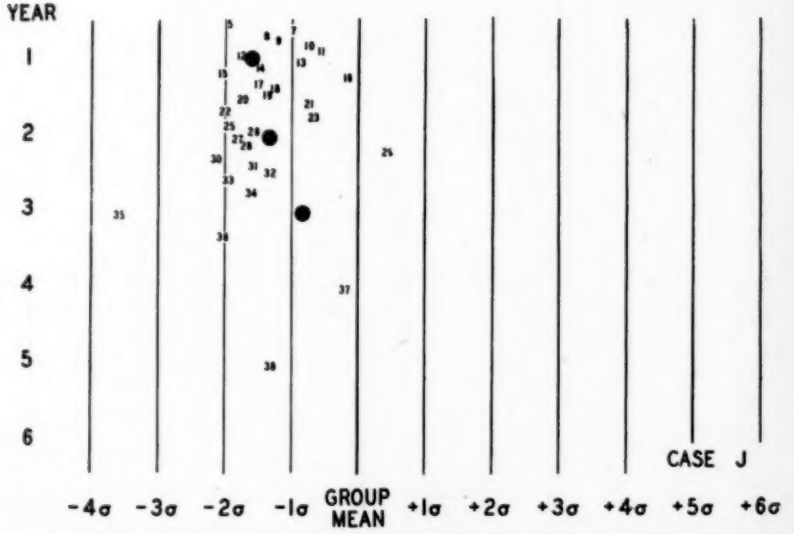
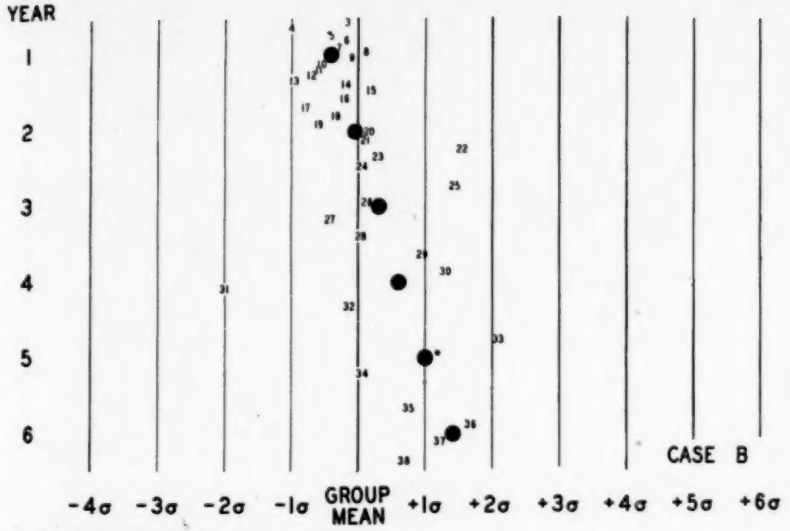
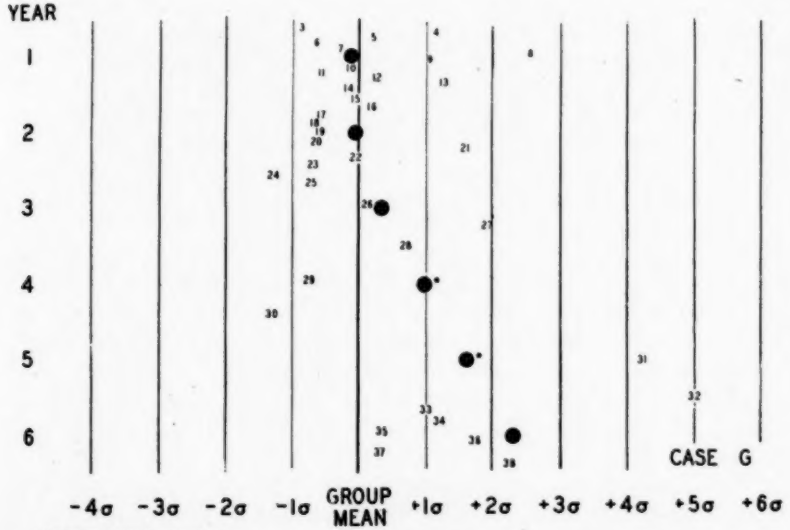


Fig. 8.—Diagram of the distribution of standard scores of the time of appearance of thirty-eight ossification centers in child J. Each number represents a specific center and the black dots represent Z score means of centers appearing during each of the three years.



*Interpolated mean.

Fig. 9.—Diagram of the distribution of standard scores of the time of appearance of thirty-eight ossification centers in child B. Each number represents a specific center and the black dots represent Z score means of centers appearing during each of the six years.



*Interpolated means.

Fig. 10.—Diagram of the distribution of standard scores of the time of appearance of thirty-eight ossification centers in child G. Each number represents a specific center and the black dots represent Z score means of centers appearing during each of the six years.

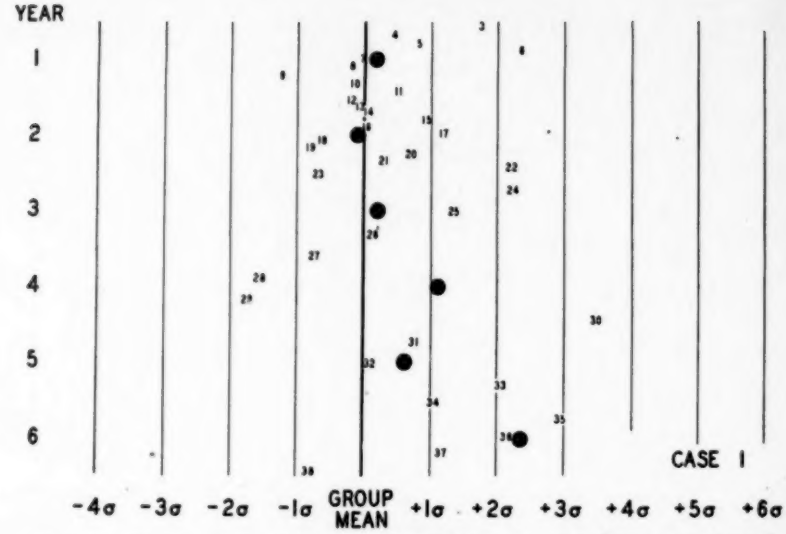
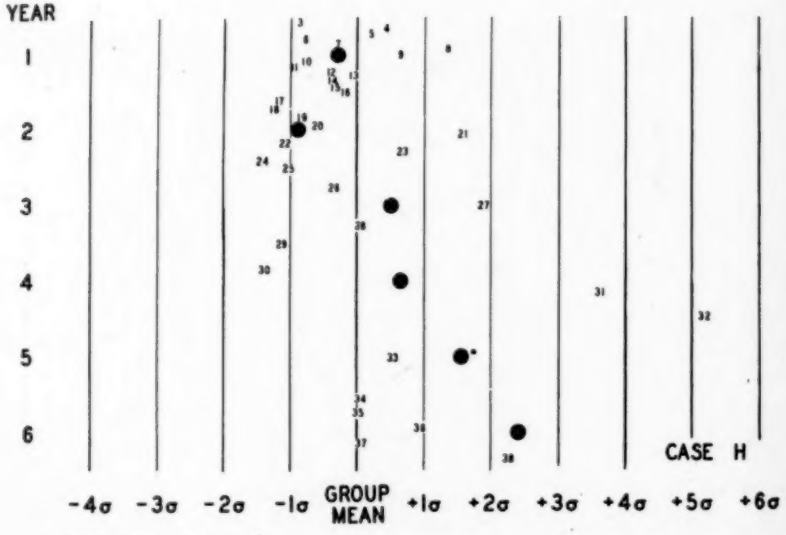


Fig. 11.—Diagram of the distribution of standard scores of the time of appearance of thirty-eight ossification centers in child I. Each number represents a specific center and the black dots represent Z score means of centers appearing during each of the six years.



*Interpolated mean.

Fig. 12.—Diagram of the distribution of standard scores of the time of appearance of thirty-eight ossification centers in child H. Each number represents a specific center and the black dots represent Z score means of centers appearing during each of the six years.

number of σ any number is from the group mean indicates how slow or fast that center appeared in relation to the group. The number of σ of such a center from the child's own mean for that year indicates how slow or fast the individual center was in relation to the child's other centers during that year.

RANGE

As one might expect, certain centers are subject to greater variability in time of appearance in relation to the group mean than others. The capitate, lateral cuneiform, capitulum, greater tuberosity of humerus, distal radius, medial cuneiform, triquetral, middle cuneiform, navicular of the foot, and lunate are the ten centers having the largest coefficient of variability.[8] Their variability is not significantly different in boys and girls.

A vast difference exists between individual children in the degree to which their ossification conforms to the group pattern. They may vary from a "tight" pattern, such as shown in Figs. 1, 2, 3, 4, and 5, to very "loose" ones, such as are shown in Figs. 10, 11, and 12. Those shown in Figs. 6, 7, 8, and 9 are intermediate; that is, neither very "loose" nor very "tight." The pattern in Fig. 4 shows considerable dispersion during the first year but is "tight" in later years. It should be noted, that while the distribution of centers in Fig. 6 is fairly "tight" in relation to the child's own yearly means, many of them are as much as three or four σ from the group mean. In other words, their order is consistent with that of the group, but the majority of the centers appearing during a given year or several years lags behind the group mean. On the other hand, the ossification centers in Figs. 10, 11, and 12 are no further from the group mean than are those in Fig. 6, but they are widely disseminated in relation to the child's yearly means.

The yearly means of each child present in themselves interesting patterns. They represent the yearly rate of epiphyseal development. The twelve children represented by Figs. 1 to 12 have been selected from the group as representing various types of epiphyseal appearance patterns. They demonstrate the way in which children vary from year to year in rates of epiphyseal onset. In Fig. 6 epiphyseal appearance during the first year was slow, as shown by the yearly means, but not nearly so slow as during the second and third years. During the next three years the rate picked up slightly but never approached the group mean. Here is a child who, for some reason not apparent from careful study, at short intervals throughout her life is markedly retarded in rate of appearance of centers. She has always been on an excellent dietary regime both qualitatively and quantitatively, has had few illnesses, has made excellent progress in height and weight growth, and shows no signs of endocrine dyscrasia. Figs. 2, 3, and 8 represent children whose centers appeared early, most of them being present by the third or fourth year. Figs. 9 and 10 represent children whose first

epiphyses appeared early but whose rates of appearance slowed markedly and consistently. Figs. 11 and 12 show children whose ossification varied irregularly without consistent trend.

The data available have made it possible to investigate the relationship of various environmental and genetic factors to such differences in ossification patterns. The following are some of the questions we have tried to answer:

1. Does rate of growth (that is, advanced or delayed ossification) affect the number of aberrant or out-of-line centers a child has?
2. Does illness tend to reduce the total rate of appearance of ossification centers?
3. Does illness produce delay in some centers and thus affect the number of slow aberrant centers?
4. Is there a genetic or familial factor which tends to make children in the same family have more similar patterns than would be found by chance?

RATE OF GROWTH

For purposes of statistical comparison we have defined an "aberrant center" as one which differs .6 standard score or more from the child's own mean for the year during which the center actually appeared. Our selection of .6 as the amount of deviation necessary for aberrance is purely arbitrary. Observation of our data suggested that as a good figure. The selection of .5, .7, or .8 would have been almost equally suitable and would not significantly change the results. Individual children had as few as four or five aberrant centers and as many as nineteen. We selected the fifteen children having the fewest aberrant

TABLE II

COMPARISON OF OSSIFICATION SCORES (TIME OF APPEARANCE SCORES) OF THE FIFTEEN CHILDREN HAVING THE FEWEST "ABERRANT" CENTERS WITH THE FIFTEEN HAVING THE MOST; THE CHILDREN HAVING THE MOST ABERRANT CENTERS ARE THE SLOWER GROWING

	NUMBER OF ABERRANT CENTERS M $\pm \sigma_M$		OSSIFICATION STANDARD SCORES		
	MEAN OF TOTAL NUMBER OF ABERRANT CENTERS	MEAN NUMBER OF SLOW ABERRANT CENTERS	MEAN OF OSSIFICATION STANDARD SCORES $\pm \sigma_M$	DIFFERENCE BETWEEN MEANS $\pm \sigma$ DIFFERENCE	SIGNIFICANCE OF DIFFERENCE
Fifteen children with fewest aberrant centers	7.47 ± 2.00	3.47 ± .96	−.31 ± .52	.37 ± .17	t = 2.15 P = .015
Fifteen children with most aberrant centers	16.53 ± 1.86	8.67 ± .87	+.06 ± .38		

P = Double tailed.

$$t = \frac{M_{x1} - M_{x2}}{\sqrt{\frac{\Sigma X_1^2 + \Sigma X_2^2}{N_1 + N_2 - 2}} \quad \sqrt{1/N_1 + 1/N_2}}$$

centers and the fifteen having the most. We then computed "ossification scores" of the two groups by determining the mean Z scores for all of the centers of the fifteen children in each of the two groups. The results are shown in Table II with the difference between the two means shown as T scores. The difference between the ossification scores of the two groups appears to be significant since there are only fifteen chances in a thousand of its being the result of chance. We are justified in assuming then that in our group the children with the fewest aberrant centers, the children who followed group order most closely, were the faster growing children in terms of new centers.

TABLE III

COMPARISON OF THE RATES OF EPIPHYSEAL APPEARANCE (OSSIFICATION SCORES) OF THE FIFTEEN CHILDREN HAVING THE MOST ILLNESS WITH THE SAME FACTOR IN THE FIFTEEN HAVING THE LEAST ILLNESS; THE CHILDREN WHO HAD THE MOST ILLNESS GOT OSSIFICATION CENTERS EARLIER THAN DID THOSE WITH THE LEAST ILLNESS

	MEAN OF TOTAL STANDARD SCORES $\pm\sigma_M$	DIFFERENCE BETWEEN MEANS $\pm\sigma$ DIFFERENCE	SIGNIFICANCE OF DIFFERENCE
Fifteen children with most illness	−.29 ± .56	.35 ± .20	t = 1.71 P = .04
Fifteen children with least illness	+.06 ± .52		

P = Double tailed.

$$t = \frac{M_{v1} - M_{v2}}{\sqrt{\frac{\Sigma X_1^2 + \Sigma X_2^2}{N_1 + N_2 - 2}}\ \sqrt{1/N_1 + 1/N_2}}$$

ILLNESS AND RATE OF GROWTH

The question of the effect of illness on rate of appearance of new centers was similarly attacked. We selected from our group the fifteen children with the most and the fifteen with the least number of illnesses and compared the means of the ossification Z scores of the two groups (see Table III). Selection of children on the basis of illness required some interpretation since severity is an important factor as well as the actual number of days of illness and frequency of illness. Degree of fever and duration were weighed equally in selecting the group. Illness varied in type among children. As was to be expected, upper respiratory disease made up a considerable bulk of it, with gastrointestinal upsets and infections and the acute contagious diseases of childhood appearing frequently. There was an occasional case of acute appendicitis, pyelitis, pneumonia, etc. Most of these diseases were not prolonged. Some of them were, however, severe.

There are only four chances in a hundred that the differences in the ossification scores for the two groups are due to chance. In our group, therefore, there was evidence that children with more illness (upper respiratory, contagious, gastrointestinal, etc.) were getting their epiphyses at an earlier age than children with little illness. Whether

rapid epiphyseal growth made them more susceptible to illness, or whether illness stimulated higher metabolism and earlier epiphysial appearance might be questioned. It is of interest that Martens and Meredith[9] found no effect of illness upon growth in body dimensions or in weight in a group of Iowa children.

TABLE IV

COMPARISON OF THE NUMBER OF ABERRANT CENTERS AND SLOW ABERRANT CENTERS FOUND IN THE TWO GROUPS OF FIFTEEN CHILDREN WITH THE LEAST ILLNESS AND WITH THE MOST ILLNESS; THERE IS NO SIGNIFICANT DIFFERENCE IN THE ABERRANCE OF THE CENTERS OF THE TWO GROUPS

	MEAN NUMBER OF ABERRANT CENTERS $M \pm \sigma_M$	DIFFERENCE BETWEEN MEANS $\pm \sigma$ DIFFERENCE	SIGNIFICANCE OF DIFFERENCE	MEAN NUMBER OF SLOW ABERRANT CENTERS $M \pm \sigma_M$	DIFFERENCE BETWEEN MEANS $\pm \sigma$ DIFFERENCE	SIGNIFICANCE OF DIFFERENCE
Fifteen children with least illness	13.7 ± 2.9			6.9 ± 1.4		
		2.0 ± 1.2	CR=1.7		$.9 \pm .7$	CR=1.3
			P= .11			P= .22
Fifteen children with most illness	11.7 ± 3.3			6.0 ± 2.0		

P = Double tailed.

$$CR = \frac{\text{Difference}}{\sqrt{\frac{(\sigma_x)^2}{N_x - 1} \quad \frac{(\sigma_y)^2}{N_y - 1}}} = \frac{\text{Difference}}{\sigma \text{ Difference}}$$

ILLNESS AND ABERRANT CENTERS

Table IV compares the number of aberrant centers in the fifteen children with most illness with the same factor in the group of children with least illness. The same children in the two groups, one with most and one with least illness, were used as when rate of epiphysial appearance was compared. Since the chances are eleven and twenty-two in a hundred, respectively, that the differences in the means are due to chance, we are not justified in presuming that in the children in this group frequency of illness has affected the order of appearance of ossification centers nor has been responsible for certain centers appearing early or late in relation to the child's other centers, although the figures suggest that the children with the most illness (who also got their epiphyses faster) had fewer aberrant centers.

In addition to comparing the number of aberrant centers in the group of children who had most illness with the number in the group with the least illness, we have compared the amount of illness occurring among the fifteen children with the fewest slow aberrant centers with that among the fifteen with the most aberrant centers (Table V). In this comparison each week, or part week, of febrile illness was considered as one illness. Thus a child sick for from one day to a week was rated as having one period of illness. If the attack lasted nine or ten days, he rated two illnesses. Whooping cough lasting four

weeks was rated four illnesses. It is, of course, a purely arbitrary procedure to equate illness by such a method. Inaccuracy is, however, inherent in any attempt to equate deviations from normal health. These results affirm those of the preceding paragraph; namely, that in the children in our group individual centers were not delayed by illness.

TABLE V

COMPARISON OF THE MEAN AMOUNT OF ILLNESS PER MONTH AMONG TWO GROUPS OF FIFTEEN CHILDREN, THE FIRST HAVING THE FEWEST SLOW TO APPEAR ABERRANT CENTERS, AND THE SECOND HAVING THE MOST; THERE IS NO SIGNIFICANT DIFFERENCE IN THE AMOUNT OF ILLNESS IN THE TWO GROUPS

	ILLNESS PER MONTH $M \pm \sigma_M$	DIFFERENCE BETWEEN MEANS $\pm \sigma$ DIFFERENCE	SIGNIFICANCE OF DIFFERENCE
Fifteen children with fewest (slow) aberrant centers*	.43 ± .12	.03 ± .34	t = .09 P = <.46
Fifteen children with most (slow) aberrant centers*	.46 ± .12		

P = Double tailed.

$$t = \frac{M_{x1} - M_{x2}}{\sqrt{\frac{\Sigma X_1^2 + \Sigma X_2^2}{N_1 + N_2 - 2}} \sqrt{1/N_1 + 1/N_2}}$$

*These are the same groups as those in Table II, since aberrancy expresses itself about equally in slow and fast centers.

These illnesses are of short duration and of course of varying severity. The fact that they apparently have not slowed growth cannot be interpreted to mean that severe and prolonged illness such as chronic pulmonary tuberculosis, nephritis, etc., might not do so.

Examination of the case histories of these children for a relationship between a specific illness of some severity and the delayed appearance of a center which should have appeared about the time of the illness yields information similar to that obtained by statistical treatment. The following are examples of the way history of illness fails to conform with delay in appearance of centers due to come in about the time of the illness.

E. C. had whooping cough at 29 months of age, with no other severe illnesses during the first four years. Her centers most delayed in appearance were middle cuneiform due according to her yearly norm at 22½ months of age and medial cuneiform due according to her yearly norm at 18 months of age. Obviously the whooping cough at 29 months of age could not have been responsible for the middle cuneiform failing to appear at 18 months of age. The first of these actually appeared at 29 months and the second at 35 months of age.

J. C. had whooping cough at 37½ months of age. The most retarded centers were (1) triquetral, due (for her) at 27.7 months of age but appearing at 40 months of age; (2) distal third toe, due (for

her) at 35.1 months of age but appearing at 41 months of age. Both of these centers should have appeared before the whooping cough and should not therefore have been influenced by its subsequent occurrence.

J. B. had severe infectious diarrhea beginning at 16 months of age and lasting for six weeks. His most delayed centers were (1) distal tibia, due (for him) at 4.6 months of age but appearing at 7 months of age; (2) distal first toe, due (for him) at 19.6 months of age but appearing at 28 months of age; (3) metatarsal I, due (for him) at 29.9 months of age but appearing at 35 months of age. The illness existing one month before the scheduled appearance of the distal first toe might well have been responsible for its delay. Since neither appearance of the distal tibia nor the first metatarsal could have been influenced by the illness, it seems not improbable that the relationship of the illness to the delay in appearance of the first metatarsal is coincidental.

R. B. had pneumonia at 33 months of age. Most delayed centers were (1) cuboid, due (for him) at .8 months of age but appearing at 2.0 months of age; (2) distal tibia, due (for him) at 4.5 months of age but appearing at 8.0 months of age; (3) capitulum, due (for him) at 8.0 months of age but appearing at 12.0 months of age; (4) distal fibula, due (for him) at 10.5 months of age but appearing at 16.0 months of age. All of these centers were not only due but actually appeared before the illness. No center due at the time of or after the illness was markedly retarded.

M. A. had appendicitis with prolonged peritonitis at 35 months of age. Most delayed centers were (1) head of humerus, due (for her) at 3.1 months of age but appearing at 5.0 months of age; (2) metacarpal, first, due (for her) at 21.3 months of age but appearing at 29.0 months of age; (3) lunate, due (for her) at 37.5 months of age but appearing at 56 months of age. The lunate due at 37.5 months of age might well have been delayed by the illness, which, however, cannot account for the other two. These cases have all been selected for presentation here on one basis only; that is, comparative freedom from illness during the first four years of life except for one fairly severe one, causing debilitation for a month or more.

The one case of diagnosible hypothyroidism in our series showed, in addition to markedly slow yearly means, an unusual number of centers appearing very late even in relation to these slow yearly means. Institution of thyroid therapy not only raised the means but appeared to reduce somewhat the number of centers which were late in relation to them. Whether this phenomenon is due to the fact that children with slower yearly means also have more slow aberrant centers or whether the thyroid deficiency is a more directly contributing factor has not been determined.

GENETIC FACTORS

In order to test Kohler's theory of familial patterns of appearance of centers, we have devised a method of comparing the degree to which the patterns of two children conform to each other. Obviously a direct comparison of Z scores is worthless since a child who was very slow in developing new centers might have all plus Z scores while one fast growing could have all minus Z scores, yet the order of the two might be identical. We therefore compared children with each other by the following means. The aberrant centers of one child were compared with those of another (in relation to the yearly means of each), and the incidence of those aberrant centers which did not coincide in the two children was expressed in percentage. Thus if child A had centers 1, 3, 7, and 10 aberrant (and slow) and child B had 1, 3, 8 and 11 aberrant (and slow), it is apparent that the children were alike in having 1 and 3 slow but different in that 7 and 10 were "out of line" in A, while 8 and 11 were "out of line" in B. Since between them they had eight centers aberrant and four of them did not coincide,

TABLE VI

COMPARISON OF THE PERCENTAGE OF ABERRANT CENTERS FAILING TO COINCIDE WHEN PAIRS OF TWINS, SIBLINGS, AND NONSIBLINGS ARE COMPARED; THE GREATEST POSSIBLE DIFFERENCE IN WHICH CENTERS ARE ABERRANT WOULD BE 100; IF ALL ABERRANT CENTERS IN TWO CHILDREN BEING COMPARED COINCIDED, THEIR PERCENTAGE DIFFERENCE WOULD, OF COURSE, BE 0

	NUMBER OF PAIRS OF CHILDREN	MEAN % OF DIFFERENCE IN ABERRANT CENTERS $\pm\sigma_M$	DIFFERENCE BETWEEN MEANS $\pm\sigma$ DIFFERENCE	SIGNIFICANCE OF DIFFERENCE
A. Siblings vs. nonsiblings				
All siblings (including twins)	25	69.3 ± 15.5	13.4 ± 3.3	CR* = 4.11
vs. nonsiblings	174	82.7 ± 10.4		p = <.0003
All siblings (excluding twins)	22	72.4 ± 12.3	10.3 ± 2.8	CR = 3.68
vs. nonsiblings	174	82.7 ± 10.4		p = <.0008
Siblings, like sex (including twins), vs. nonsiblings	12	62.2 ± 17.1	20.5 ± 5.2	CR = 3.94
	174	82.7 ± 10.4		p = .0010
Siblings, like sex (excluding twins), vs. nonsiblings	9	67.4 ± 13.4	15.3 ± 4.8	CR = 3.19
	174	82.7 ± 10.4		p = .0064
Siblings, unlike sex, vs. nonsiblings	13	75.9 ± 10.1	6.8 ± 3.0	CR = 2.55
	174	82.7 ± 10.4		p = .022
B. Siblings vs. siblings				
Siblings, like sex (including twins), vs. siblings, unlike sex	12	62.2 ± 17.1	13.7 ± 5.9	CR = 2.32
	13	75.9 ± 10.1		P = .04
Siblings, like sex (excluding twins), vs. siblings, unlike sex	9	67.4 ± 13.4	8.5 ± 5.6	CR = 1.53
	13	75.9 ± 10.1		P = .16
C. Nonsiblings vs. nonsiblings				
Nonsiblings, unlike sex, vs. nonsiblings, like sex	86	82.4 ± 11.3	.6 ± 1.6	CR = .42
	88	83.0 ± 9.4		P = .66

P = Double tailed.
p = Single tailed.
*See footnote to Table IV.

they were described as differing in 50 per cent of their aberrant centers. Had center 3 been slow aberrant in A but fast aberrant in B, these two would also have been different, raising the number of differing aberrant centers to six out of eight, or 75 per cent. We have thus compared 174 pairs of children who were not siblings selected at random with twenty-five pairs of siblings (like sexed and unlike sexed) and with three pairs of monozygotic twins. Table VI compares the mean percentages of differences in aberrant centers in these groups.

TABLE VII

THE MEANS* OF CORRELATION COEFFICIENTS OF THE Z SCORES OF THE THIRTY-EIGHT CENTERS IN TWINS, SIBLINGS AND NONSIBLINGS

CATEGORY	NUMBER OF CHILDREN	MEAN PEARSONIAN SCORE
Monozygotic twins	6	+.82
Total siblings	24	+.32
Total nonsiblings	24	−.08

*Using formula $M_r = \sqrt{\frac{\Sigma r^2}{N}}$ from Garrett, Henry E.: Statistics in Psychology and Education, New York, 1937, Longmans, Green & Co., p. 284.

We have also compared likeness of ossification pattern in siblings, nonsiblings, and monozygotic twins by means of the correlation technique. Twelve siblings were selected, representing varying degrees of likeness of ossification pattern from greatest to least degree and the Z scores of their centers correlated by means of the Pearsonian technique without regard to yearly means. Twelve liked sexed and twelve unliked sexed siblings were used. Twelve nonsiblings, Z score scores similarly selected, were correlated. Pearsonian r's for three pairs of monozygotic twins were also calculated. The results are shown in Table VII. Here again the likeness of the patterns of monozygotic twins stands out with a mean r of +.82. Siblings excluding twins yielded a mean r of +.32 while the mean r for the nonsiblings was −.08. This treatment of the data strengthens our conclusion that there is a genetic factor in ossification pattern.

SUMMARY AND CONCLUSIONS

We have determined the time of appearance of each of thirty-eight selected ossification centers from serial x-rays of the left side of the body. Eighty-four children composed the study. The Z scores of the time of appearance of each of these centers has been compared to the group means and to the child's own mean for each year. Some children's centers present a pattern rather consistent with the group pattern while others deviate greatly from it. Faster growing children had fewer "out-of-line centers" than did slow-growing ones. Incidence of the usual childhood diseases was greater among the fast-growing than among the slow-growing children. Incidence of such illness in our series has not delayed the centers which were about to

appear at the time of illness nor has it caused a greater incidence of centers "out of line" with the group or the child's own pattern. There is a greater likeness in ossification patterns among siblings than among nonsiblings and among like-sexed siblings as compared with unlike sexed siblings. Monozygotic twins show even more clearly this genetic factor in ossification pattern. Our work corroborates Kohler's, Buschke's, and Pryor's observations on the importance of the genetic factor in ossification pattern but does not support the contentions of Francis and Todd, that the centers' appearance is easily influenced by acute illness. Our findings do not imply, however, that the genetic factor is the only one of importance. The differences in the patterns of monozygotic twins, while less than between siblings, indicate definitely the great importance of other factors. A future paper will deal with the significance of nutrition. No conclusions as to effect of chronic disease were derived from this study, since we have dealt here only with acute or subacute conditions.

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A CASE OF VITAMIN D DEFICIENCY ASSOCIATED WITH CIRRHOSIS OF THE LIVER AND A DYSCRASIA OF CALCIUM AND PHOSPHORUS METABOLISM

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THE purpose of this paper is to present in detail the clinical history, physical findings, calcium and phosphorus balance studies, and necropsy observations of an 18-year-old boy afflicted with a deranged metabolism of calcium and phosphorus.

CASE REPORT

Abstract of Medical History from Birth to Death at 19 Years.—The patient, F. D., was first observed by me when he was 18 years of age. He had been a semiinvalid all his life. He was born in a tenement district of the East Side, New York, the last of nine children of Italian parentage. Three of the nine children died in infancy of an undetermined cause.

While the child was in utero the mother was chronically ill with weakness, anorexia, bronchitis, and repeated attacks of vomiting. The birth was normal. Due to her debilitated condition, the mother had a very scant flow of milk; therefore, cow's milk and sugar constituted the chief food of the infant. All breast feeding was discontinued at 9 months of age. At 2 years of age his diet consisted of farina, milk, bread, coffee, and tea. He had measles and scarlet fever, both without known complications.

He was admitted to the Post-Graduate Hospital, New York City, March 26, 1916, when he was 24 months old. The chief complaint was cough and fever. The physical examination showed the following positive findings: The head was symmetrical with the fontanels closed and the parietal eminences enlarged. The circumference of the occiput was 16¼ cm. as compared with the circumference of the chest, which was 16 cm. at the nipple line. Marked beading of the ribs with a "pigeon shape" was noted. Râles were heard at both bases. The abdomen was distended, with the liver palpable one inch below the costal margin. The extremities were fairly well developed, with marked enlargement of the epiphyses. The temperature was 102.8° F.; weight on admission was 15 pounds, 1 ounce; on discharge, 14 pounds, 15 ounces. The sole therapy consisted of 15 c.c. of castor oil every three or four days and boric acid eyewash. Unfortunately, in 1916 modern rachitic therapy was not known. After seven weeks in the hospital he was discharged improved on March 26, 1916, the diagnosis being rickets.

Having received no specific medication, this debilitated and rachitic child continued to live in the tenement district of New York City. A weakness of his extremities persisted which the father describes as softness of the bones, and he was unable to walk until nearly 8 years of age. He first attended a school for cripples in his ninth year. This institution sent its children to the country for three months each summer. While in the country they wore a minimum of clothing and were exposed as much as possible to the sun's rays. Although he went to the country a cripple, scarcely able to walk, he returned three months later able to run with his playmates. Pigmentation, resulting from exposure to the sun, was so marked that his mother did not recognize him.

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In 1928 and again in 1930, the patient fell while walking and fractured the right femur, with a spontaneous but somewhat delayed union of the bone in each instance. In 1928 and 1930, he was observed in Bellevue Hospital. The rachitic contour of the chest was detected, together with the abnormality of the teeth. In 1928 the blood serum calcium was 10 mg. per 100 c.c. (normal range, 9 to 11.5) and the serum phosphorus, 2 mg. per 100 c.c. (normal range, 5 mg. in infants and children and 3.7 mg. in adults.)[1]

Metabolism studies were conducted in a medical ward of Bellevue Hospital. He was admitted April 10, 1932, and discharged June 21, 1932. Calcium and phosphorus balance studies showed an abnormally high excretion of these elements in the urine. At this time he was 18 years of age and was in relatively good health.

Viosterol therapy was started in the hospital and continued for three months thereafter; the dose was 50,000 U.S.P. units daily for twelve days while in the hospital and 2,500 units three times daily for the succeeding three months. All viosterol was given by mouth. Clinical and roentgenogram examination showed no evidence that viosterol was of any benefit. In January and again in March, 1933, the patient suffered from what was described by the family as a severe cold. On March 24, 1933, the blood showed 3,400,000 red blood cells and the hemoglobin was 65 per cent. About July 1, 1933, he developed an acute upper respiratory infection complicated by extensive pleural effusion of the right side. He was again observed in Bellevue Hospital. The course was fulminating and he died Aug. 29, 1933, at the age of 19, of acute pulmonary tuberculosis. At the time of the metabolism studies in 1932, the case was intensively studied and the following data, except for the autopsy report, were obtained at that time.

Physical Examination at 18 Years of Age.—The significant positive findings were related to the skeletal system. (1) All the teeth were markedly hypoplastic, with definite roughening of the enamel. There was a moderate amount of caries and a marked absence of tooth substance. The teeth were very loosely imbedded in their sockets. There was an irregular arrangement and poor occlusion surface. There was a moderate amount of peridental disease, or pyorrhea. (2) The skeletal system was asymmetrical. This was shown by protuberances of the right posterior parietal and right frontal region, and a prominence of the right side of the thorax just below the clavicle as compared to the left. (3) The right leg showed a deformity due to an old fracture of the right femur and a partial ankylosis of the right ankle joint (see Figs. 1 and 2).

The heart, lungs, abdomen, and genitals were normal. The blood pressure was 110/80. From the point of view of intelligence the patient would probably be classed a dull normal.

Laboratory Data.—The height was 62 inches; weight was 110 pounds; temperature, pulse, respiration, urine, and blood count were within normal limits. The blood Wassermann was negative. The blood chemistry on April 23, 1932, showed serum calcium 10.2 mg. per 100 c.c. and serum phosphorus 1.9 mg. per 100 c.c. The blood serum phosphatase was 10.0 on Feb. 3, 1932, and 11.0 on April 26, 1932. (The serum phosphatase in normal adults ranges from 1.5 to 4 units per 100 c.c. [average, 2.7] and in normal children, 5 to 12 units.)[1]

Roentgenograms (Fig. 3) showed a generalized deficiency of calcium salts in all of the bones, with absorption of the cortex. X-rays of the mandible showed rarefaction as in the other bones in the body. The angle of the mandible was more obtuse than normal. Marked malocclusion was obvious. The teeth showed extensive notching, particularly of the incisors, and deficient calcification was present.

The response of the ulnar, median, and radial nerves to galvanic current was within normal limits. The basal metabolism was normal.

The Plan of Conducting the Calcium and Phosphorus Metabolism Studies.—After a preliminary period of one week, the metabolism of calcium and phosphorus was

Fig. 1.—Patient F. D., showing deformities of the bony skeleton.

Fig. 2.—Shows the extreme irregularity and hypoplasia of the teeth.

Fig. 3.—Roentgenogram of the radius and carpal and metacarpal bones, showing a generalized deficiency of calcium salts, absorption of the cortex, and the defective development of the epiphyses.

studied in nine periods of four days each. The plan was to determine the intake and output of calcium and phosphorus on three different types of diet: normal, very low, and very high intakes. The calcium in the food ranged from a low of 0.112 Gm. to a high of 1.983 Gm. per day. The phosphorus in the food ranged from a low of 0.643 Gm. to a high of 2.344 Gm. per day. The protein intake was between 50 and 109 Gm. per day. One-half of a dram of fluid extract of cascara followed by 10 gr. of carmine was used to differentiate between two successive fecal periods.

During the first three periods the subject was confined to bed, but allowed bathroom privileges. During the last six periods, he was up and about the ward and fairly active. A standardized preparation of viosterol* in a dosage of 5 c.c., or 50,000 U.S.P. units per day, was administered during the last three periods of the experiment.

Methods.—The calcium and phosphorus in the diet were calculated from tables given by Rose.[2] It has been stated previously by this laboratory[3] that "the calculated amount varies from the analyzed amount, both above and below, but the variation does not exceed 5 per cent. Therefore, it is believed that the intake recorded represents the actual amount of calcium and phosphorus ingested with a maximum error of 5 per cent." The calcium in the urine was determined by the method of Shohl and Pedley.[4] The phosphorus in the urine was determined by the method of Fiske and Subbarow.[5] The feces were dried, digested with sulfuric and nitric acid, and the calcium and phosphorus were determined in the same way as in the urine. The serum calcium was done by the method of Kramer and Tisdall[6] as modified by Clark and Collip.[7] The phosphatase determinations were made through the courtesy of Dr. Bernheim of the New York Hospital by the method of Bodansky.[8]

Results of Metabolism Studies.—These are presented in Table I, and the same material is arranged graphically in Chart 1. The patient could not be kept on a positive calcium balance on 0.46 Gm. per day. However, on a calcium intake of 2.0 Gm. per day, he stored approximately 1 Gm. or one-half of this very high intake. When an exceptionally low calcium diet of 0.11 Gm. was instituted, he excreted 0.3 Gm. per day. The average negative balance on this minimum intake was 0.245 Gm. When calculated per kilogram of body weight, the daily negative balance was 0.0049 Gm. per kilogram. The average negative balance of 13 normal controls calculated by Bauer, Albright, and Aub[9] on a minimum calcium intake was 0.0023 Gm. per kilogram. This means that the subject was losing calcium at twice the normal rate.

Chart 1 shows graphically the relatively constant urinary or endogenous excretion of calcium irrespective of the intake. The maximum variation was 0.14 Gm. per day, although the variation in calcium intake was from 0.11 to 2.0 Gm.; that is, the highest calcium intake was eighteen times the lowest, but the excretion via the kidneys was practically constant. Furthermore, whereas the normal individual on 0.4 Gm. intake excretes only about one-fourth of the ingested calcium via the kidneys, the patient reversed this ratio and excreted more calcium through the urine than through the feces.

In general, the balances of phosphorus followed those for calcium. The chief differences were as follows: (1) the deranged mechanism of excretion was accentuated; that is, an even greater proportion of phosphorus was excreted via the kidneys than in the case of calcium; (2) Except for the two periods of very low ingestion, the patient remained on a positive phosphorus balance. Thus, on a normal phosphorus diet there was a slight positive balance, but in the case of calcium there was a negative balance on a similar intake.

*Mead Johnson & Co.

TABLE I

CALCIUM AND PHOSPHORUS BALANCES

	DATES INCLUDED	NUMBER OF DAYS	CALCIUM*				PHOSPHORUS*				REMARKS
			INTAKE†	OUTPUT			BALANCE	INTAKE†	OUTPUT			BALANCE	
				URINE	FECES	TOTAL			URINE	FECES	TOTAL		
I	April 22												
	26	4	0.464	0.303	0.222	0.525	−0.061	1.245	0.977	0.248	1.225	+0.020	April 23: Serum calcium, 10.3
II	26												April 23: Serum phosphorus, 1.9
	30	4	0.459	0.340	0.236	0.576	−0.117	1.253	0.840	0.267	1.107	+0.146	April 26: Serum calcium, 10.6
III	30												April 26: Serum phosphorus, 2.3
	May 4	4	0.112	0.320	0.048	0.368	−0.256	0.643	0.675	0.103	0.778	−0.135	April 26: Serum phosphatase, 11
IV	4												
	8	4	0.112	0.300	0.047	0.347	−0.235	0.643	0.533	0.185	0.718	−0.075	
V	8												
	12	4	0.454	0.406	0.093	0.499	−0.045	1.190	0.639	0.204	0.843	+0.347	
VI	12												
	16	4	1.983	0.316	0.638	0.954	+1.029	2.121	0.795	0.233	1.028	+1.093	
VII	16												
	20	4	1.977	0.343	0.665	1.008	+0.969	2.344	0.938	0.260	1.198	+1.146	
VIII	20												
	24	4	1.972	0.367	0.569	0.936	+1.036	2.104	0.990	0.216	1.206	+0.898	Viosterol‡
IX	24												
	28	4	1.972	Specimens of stool and urine not saved				2.104					May 26: Serum calcium, 10.5
													May 26: Serum phosphorus, 2.0
X	28												
	June 1	4	1.828	0.442	0.294	0.736	+1.092	2.132	0.980	0.213	1.193	+0.939	Viosterol‡

*All data given as average grams per day for the period.

†Calculated from Sherman's mineral tables as given in Rose's Laboratory Handbook for Dietetics.[3]

‡Mead's standardized preparation of viosterol: 5 c.c. = 50,000 U.S.P. units daily.

Although 5 c.c. of a solution of viosterol containing 10,000 units of vitamin D per gram was given each day for the last three periods, or for twelve days, there was no evidence that it influenced the calcium and phosphorus balances.

Autopsy.—Necropsy was performed within six hours after death. The primary anatomic diagnoses were: Pulmonary tuberculosis, caseous right lower lobe; chronic fibrinous pleuritis with effusion, left; and lobular pneumonia, bilateral.

The general anatomic diagnoses were: Liver, atrophic cirrhosis and phlebosclerosis, and thrombosis of the portal veins; diaphragm, diaphragmatic peritonitis; spleen, splenomegaly; gastrointestinal tract, hyperplastic Peyer's patches and ulceration of the ileum with overlying peritoneal tubercles; rectum, congestion; skin, brown pigmentation; bone, hypoplasia of the cortex of the calvarium, ribs, sternum, and vertebrae; brain, pial edema; general, emaciation and icterus; nodes, tuberculosis of the peribronchial lymph nodes.

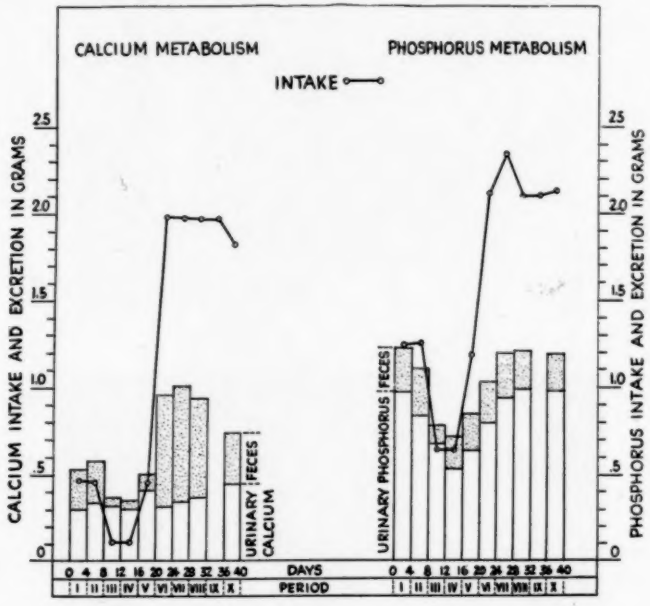

Chart 1.

The liver surface was very irregular and presented a hobnail appearance. On section there was a marked increase of interstitial connective tissue which appeared to be continuous with the capsule and presented a grossly irregular lobulated architecture to the organ. Histologically, the liver parenchyma was divided into many lobules of varying size by dense bands of fibrous connective tissue. Imbedded in these bands were many dilated blood spaces and actively proliferating bile ducts. The liver cords were irregular in outline and stained poorly. The histologic diagnosis was portal cirrhosis (see Fig. 4).

Two parathyroids were isolated. They were normal grossly and histologically (see Fig. 5). A search was made for additional parathyroid tissue and none was found. (The failure to find hyperplastic thyroid tissue does not exclude its presence as it may have been aberrant in its position.)

Fig. 4.—Photomicrograph of the liver, showing portal cirrhosis.

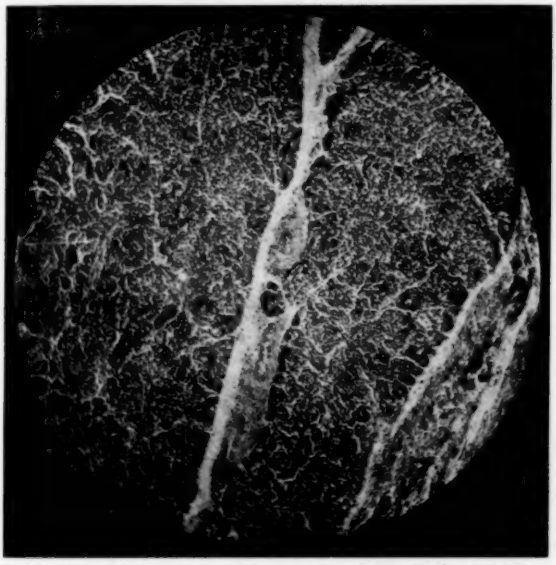

Fig. 5.—Photomicrograph of one of the parathyroid glands, showing normal structure. The tissue was fixed in formalin, imbedded in paraffin, and stained with hematoxylin and eosin.

A.

B.

Fig. 6.—*A*, Photomicrograph of a "normal" ground unstained bicuspid tooth showing good calcification of the dentine and enamel. *B*, Photomicrograph of the bicuspid similarly prepared showing severe hypoplasia of the enamel and many interglobular spaces in the dentine at the dentino-enamel junction.

The kidney on microscopic examination showed numerous small deposits of calcium which appeared to be in the interstitial tissue outside the tubules. The arteries showed an intimal thickening.

The bones displayed the asymmetry of the skeleton previously described in the physical examination. The calvarium, ribs, sternum, vertebrae, and mandible showed a definite thinning of the cortex. The red marrow of the calvarium, ribs, sternum, and vertebrae was hyperplastic and histologically actively regenerating.

Grossly, all the teeth exhibited the changes previously mentioned. In the upper jaw there were missing one bicuspid and three molars; in the lower jaw five molars and one bicuspid. Ground, unstained sections of a bicuspid and hematoxylin and eosin sections of a molar were prepared. The dentine was riddled with interglobular spaces closely approximating the dentino-enamel junction (the oldest part of the tooth), and the enamel was markedly hypoplastic. A ground, unstained section of the patient's bicuspid is shown in Fig. 6*B* and similarly prepared section of a normal individual in Fig. 6*A*.

DISCUSSION

The Possible Relation Between Cirrhosis of the Liver and Vitamin D Deficiency in This Case.—There is excellent experimental evidence that liver pathology increases the requirement for vitamin D. Heymann[10] ligated and transected the common bile duct in rats 3 to 4 weeks of age, and severe obstructive biliary cirrhosis developed within three weeks. To cure rickets in rats in which biliary cirrhosis had been thus induced, from ten to twelve times as much vitamin D was required as in comparable animals with rickets but with no cirrhosis. When severe degenerative changes were provoked in the liver of rats with carbon tetrachloride, two to three times as much vitamin D was required to cure rickets in these animals as compared to animals with rickets but without liver degeneration from carbon tetrachloride.

Three infant cases of severe rickets associated with biliary cirrhosis have been described by Gerstenberger,[11] and one case of hepatic osteomalacia has been reported by Ask-Upmark.[12] The observation that the liver of F. D. was one inch below the costal margin when he was hospitalized for rickets at 2 years of age suggests a possible cirrhosis even at this early age. The animal experimental evidence and the case reports of human beings recorded by others indicate that cirrhosis of the liver may have been an important factor in the development of vitamin D deficiency in this case.

The Relationship Between Vitamin D Deficiency and the Development of the Teeth.—Klein[13] induced typical enamel hypoplasia in swine on a rickets-producing diet. Mellanby[14, 15] has demonstrated in dogs that rickets causes an imperfect calcification of the dentine as indicated by many interglobular spaces. In addition, rachitic dogs tend to have irregular alignment of the teeth resulting in malocclusion. F. D. manifested all three of the rachitic stigmas respecting the teeth; namely, hypoplastic enamel, interglobular spaces in the dentine, and malocclusion.

The Relation Between Vitamin D Deficiency and Parathyroid Activity.—That a deficiency of vitamin D results in a hyperplasia or hyperactivity of the parathyroid bodies is substantiated by many experimental and clinical observations. This relationship has been very completely surveyed by Thomson and Collip.[16] The outstanding facts are as follows: (1) Vitamin D resembles the parathyroid hormone in that both tend to raise or maintain the blood calcium; (2) both vitamin D and parathyroid hormone mitigate the symptoms of tetany developing after parathyroidectomy; the subsidence of symptoms is associated in each instance with a rise in blood calcium; (3) rickets in the rat,[17] fowl,[18, 19] and man [20, 21, 22] provokes a hyperplasia of the parathyroid glands.

Histologically, there was no detectable hyperplasia in the two parathyroid glands which were studied. But there is a multiplicity of evidence that the rickets in infancy was followed by a compensatory hyperfunction of the parathyroids. The data supporting a diagnosis of secondary hyperparathroid disease may be summarized as follows:

1. The entire bony skeleton was extensively decalcified and the bones showed the characteristic thinning of the cortex. The bones were very fragile, as indicated by the pathologic fractures occurring at 13 and 15 years of age.

2. The blood serum phosphorus was low (2 mg. per 100 c.c.). The blood serum phosphatase was high (10.5 Bodansky units).

3. The endogenous excretion of calcium was twice that of normal controls[9] when calculated in grams per kilogram.

4. There was typical inversion of the excretory ratio for calcium and phosphorus; that is, normally four parts of these elements are excreted in the feces to one part in the urine, but in the patient this ratio was reversed.

5. The calcium and phosphorus balances were not influenced by vitamin D therapy, and the clinical picture remained unchanged during the succeeding year despite persistent vitamin D therapy. However, this patient might have responded to 150,000 or more units of vitamin D daily, as did the patient of Albright, Butler and Bloomberg.[22]

6. Many calcified areas were found in the kidneys at autopsy.

The important features of this case which are against a diagnosis of secondary hyperparathyroidism are: (1) the normal serum calcium, (2) the absence of typical bone cysts, and (3) the failure to find evidence of hyperplasia or tumor of the parathyroids at autopsy.

Since the exact mechanism of deranged calcium and phosphorus metabolism in this case is not clear, it is considered desirable to leave the question open at the present time.

SUMMARY

A case report of a boy, 18 years of age, with an intrauterine history of chronic illness on the part of the mother and a diet definitely de-

ficient in minerals and vitamins during the first few years of life, is presented. There was advanced clinical rickets at 2 years of age associated with a moderate enlargement of the liver. No specific therapy was given until the child was 9 years old, when he was sent to the country for the summer and a marked improvement in walking ability followed extensive exposure to sunshine.

At 18 years of age metabolism studies showed a dyscrasia in calcium and phosphorus metabolism which has been described in detail. Death occurred at 19 years from pulmonary tuberculosis.

Necropsy observations which were pertinent to the case history showed that the dentine of the teeth was riddled with interglobular spaces and that the enamel was very hypoplastic. The bones showed a definite thinning of the cortex and the red marrow was hyperplastic. The two parathyroid glands which were isolated were normal, grossly and histologically. The lived displayed advanced portal cirrhosis.

I am especially indebted to Dr. E. Shorr, Dr. H. B. Richardson, and Dr. E. F. Du Bois, of the faculty of medicine (Cornell) for their encouragement and guidance throughout the course of this work; to Dr. C. Bodecker, Professor of Oral Histology and Embryology, Columbia University Dental College, for the preparation and interpretation of the microscopic sections of the teeth; to Dr. E. Applebaum for the photomicrographs of the teeth; and to Dr. A. Rottine and Dr. Symmers of the Department of Pathology, Cornell (Second Division), Bellevue Hospital, for a very complete autopsy report.

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STUDIES IN HORMONE THERAPY

I. The Evaluation of Growth Hormone Treatment

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THE following paper is a report of a method which attempts to measure the effectiveness of growth hormone treatment in physically and mentally retarded children. The clinical cases chosen were children from an institution for the training of high-grade morons and borderline defectives (Wayne County Training School, Northville, Mich.). Over a period of years growth retardation in a number of these children has been treated with pituitary growth hormone (antuitrin growth*). In the course of the investigation it became apparent that the results obtained could not be satisfactorily measured with the methods commonly used; that is, by comparing increments of height and weight during the period of treatment with theoretical normal increments for corresponding age. The following study was undertaken to find means for evaluating more accurately successes and failures of treatment of retarded children with growth hormone.

Terminology.—In recent years psychologists perhaps more than physicians have investigated the somatic and mental aspects of growth and development in human beings; one outstanding example of such studies is the "Harvard Growth Study.[1]" Nearly all students of growing children use the two terms growth and development. In this paper we follow Courtis'[2] interpretation, ". . . growth will be used more frequently than development when reference is made to some single and simple aspect of development, as growth in height, or weight, or intelligence. Nevertheless, I shall speak of the development of height or intelligence also, when I have the process as a whole in mind." Since the present study deals with the treatment of undersized children by growth hormone, we shall consider here only growth in height.

To discuss the influence of treatment upon growth in height we shall use the term modification. Courtis says: "When change occurs within change itself, when growth already underway is affected by the play of a particular environmental force, the change in the growth will be called modification!" Hormone treatment involves the introduction of an external agent into the body. If growth is thereby altered, the hormone used may be classified, therefore, as an agent which modifies growth. Since the present study is concerned with individuals who

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*Parke, Davis & Co.

show pathologic growth, for example, retardation of growth in height, the modification of their growth by specific treatment may appear in two forms: (1) The treatment may be successful, in which case growth in height will be accelerated to a degree to become equal to the rate of growth in a normal individual or even surpass this rate to regain the previous loss in growth; (2) or the treatment may fail entirely or be only partially successful, in which case the rate of growth will continue at the previous pathologic rate or be but slightly accelerated.

Methods of Measurement.—The common method of measuring growth in a child is by anthropometry. There are standard tables in use which give the height, weight, and certain other average measurements for the various ages from the infantile to adult period. There are many reasons given in the literature for discarding these standard tables. Our reason is concerned with the purpose of this study. The measurement of the influence of growth hormone therapy upon an individual's body build is a secondary question in the study here reported, our interest being primarily concerned with finding satisfactory ways of measuring retardation in height growth and acceleration which might take place under treatment. We needed, therefore, measurements which gave average values of growth in height for normal children and a simple method to record it for comparative study with pathologic material. We are primarily interested in the modification taking place in the growth in height. Any tables using a height-weight index introduces a variable—weight—which differs quite widely, especially in individuals showing pathologic growth. The same objection holds true for the use of Wetzel's[3] grid method by defining first the body build.

Psychologists have accumulated data to define the growth in height, weight, intelligence, etc., corresponding to chronological age. In compiling standard tables for height, for example, the average values measuring height in a large group of children of various age levels have been expressed in units of time instead of units of length—speaking of height age at a given chronological age. One has to point to the handicap of this method in securing data which may be correct if one is dealing with a large group of children. Individual growth, however, is shown to fluctuate markedly from these average values, especially with regard to the increased rate of growth during certain periods. The Harvard studies, therefore, employed the method of "repeated measurements of the same individuals over a period of several years." The data collected by this method are not numerous enough yet to be used generally. In the present study we used the tables of Olson and Hughes.[4] The error which may occur by the use of such tables is not too great for the purposes of the present investigation, since this study is concerned with individuals who vary abnormally in height from all values given in all standard tables. The interest of this investigation is confined to finding a way to measure the amount of "modification" taking place during treatment.

Methods of Recording.—One of us (A. A. S.) has for several years made use of the age unit method of Olson in mentally retarded children. The method is shown in Fig. 1, presenting the development in height and weight of the patient in our Case 1. To explain this method we follow Olson:

> . . . In order to portray growth data collected in many types of units (inches, pounds, etc.) in an understandable manner, it is desirable to translate all measurements into a common unit. One of the simpler ways of doing this is to take the raw measurement and to convert it into the age value to which it corresponds. Under this plan, one may refer such diverse things as height in inches, weight in pounds, number of teeth erupted . . . to a common scale and speak of height ages, weight ages, dental ages. . . . One should avoid thinking of the age equivalent as a norm or standard which children are expected to attain. . . . The age unit method does not give information on the status to which the child is going in the various qualities. . . . It should also be noted that the age unit principle translates unequal units of the original measure into equal units of age, or, conversely, constant physical units have unequal age equivalents . . . In plotting life age (Fig. 1—C.A., chronological age) against any derived age, the effect is to make all growth a straight line in terms of the age

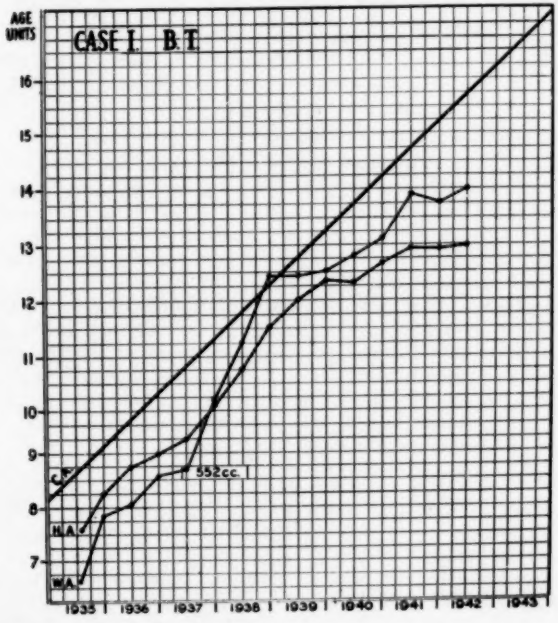

Fig. 1.—Graphic representation of the weight and height growth of B. T. during eighth to fifteenth years. Growth hormone (antuitrin growth) was administered from June, 1937, to October, 1938, a total of 552 c.c. The response of both weight age and height age curves during and for a short time following treatment is evident. The institution of hormone therapy arrested a sharp divergence of both height age and weight age lines from the chronological age line (C. A.). Divergence is resumed after hormone therapy was discontinued.

principle irrespective of the form of the curve in original units. This is, however, probably an advantage for some purposes since deflection at once is symptomatic of periods of plateau and spurt.

Presentation of Clinical Cases.—We present briefly the case histories of four children whose case records illustrate not only a favorable response to growth hormone therapy, but also illustrate quite clearly the advantages of measuring the modification of growth as outlined above.

CASE 1 (Fig. 1).—B. T., admitted at the age of 8 years (1935); white girl of American parentage; parents and siblings feebleminded; normal birth; whooping cough during childhood.

Medical Examination.—Mottling of skin of the extremities; hypermobility of joints; flat feet; visceroptosis; partial ptosis of lids; hemiatrophy of face.

Psychologic Data.—Mental age, 5 years, 10 months; I.Q., 69.

Diagnosis.—Mental deficiency (familial type); retarded growth.

Treatment.—Following an observation period of approximately two years, during which time there was a definite divergence of her height age (H.A.) and weight age (W.A.) from her chronological age (C.A.) line, she was given, in a period of fourteen months, 552 c.c. of growth hormone as charted. The response is unmistakably indicated by a convergence of the weight and height age lines toward the chronological age line. This favorable course persisted for some months after treatment stopped, but eventually the height and growth curves again diverged from the chronological age line.

CASE 2 (Fig. 2).—J. R., admitted at the age of 7 years (1937); white boy of American parentage (Irish ascendants); parents feebleminded. Normal birth, slow development; little information about early childhood.

Medical Examination.—Small stature; growth retardation.

Psychologic Data.—Mental age, 4 years, 8 months; I.Q., 62.

Diagnosis.—Mental deficiency (familial type); possible hypopituitarism.

Treatment.—After an observation period of one year, during which time his height age curve deviated very definitely from his chronological age curve, this boy was given 225 c.c. of antuitrin growth in a period of ten months. Fig. 2 shows a definite change in the height age curve with failure of the weight age curve to follow suit. Treatment was then interrupted for nearly a year with a rather marked divergence of the height age curve. Administration of antuitrin growth again, 100 c.c. in a period of nine months,* caused the height-age line to converge again until it paralleled the chronological age line, this time the weight-age line showing an even greater convergence than the height-age line. Following the second interruption of therapy, the height- and weight-age lines again became divergent with respect to the chronological age line.

CASE 3.—J. N., admitted at the age of 8 years (1938); white boy of American parentage; parents of average intelligence. Premature birth (seven months), pedal presentation, asphyxia, artificial respiration for several hours; chicken pox and pneumonia during childhood.

Medical Examination.—Small stature; growth retardation; weakness of both musculi recti externi; hypotonus of abdominal muscles.

*It has been observed,[6] that repeated administration of growth hormone to patients led rather quickly to a loss of its ability to promote increased retention of nitrogen and calcium. A rest of six to eight weeks from treatment restored the patient's original response, which was, however, again soon lost on repeated administration of the hormone. We attempted to overcome this feature by administering the hormone for ten consecutive days (2 c.c. per day) followed by fifty days' rest from treatment. This scheme of injections is referred to in the text as "special method" of treatment.

Psychologic Data.—Mental age, 4 years, 2 months; I.Q., 51.

Diagnosis.—Mental deficiency (birth injury type); possible hypopituitarism.

Treatment.—Because the patients J. N. and J. R. (Case 2) were so nearly identical in height, age, and weight when our study of them began in 1937, it was decided to hold J. N. as the untreated control. Not that we had any mistaken notions on the validity of results from such a control. This decision did, however, lead to interesting observations. Fig. 3 shows that J. N.'s height-age curve diverged from that of the treated patient, J. R., during a period of three years.

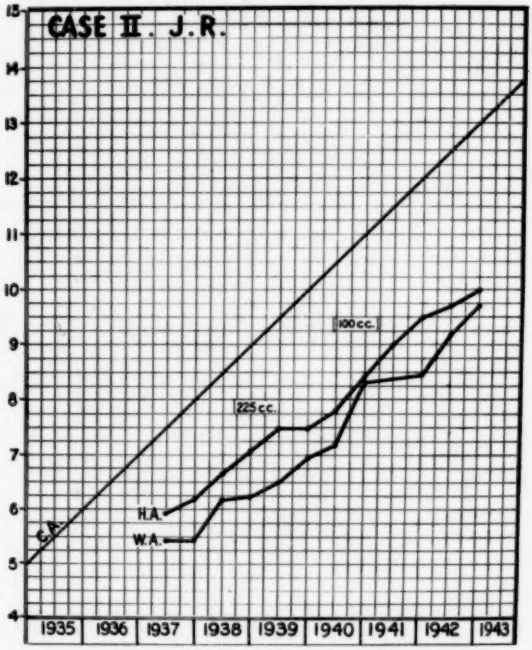

Fig. 2.—The patient, J. R., came under observation in 1937, when he was just under 6 years of age. His height and weight were at that time 1½ and 2 years, respectively, below his chronological age. A year's observation which included an adequate diet, regular hours of sleep and recreation, plus dental care and medical supervision did not cause his height age and weight age lines to converge toward his chronological age line. Growth hormone (antuitrin growth) given from August, 1938, to July, 1939, a total of 225 c.c., caused a perceptible upswing of the height age line, but did not affect the weight favorably. A second administration of the hormone, 100 c.c., over a period of ten months appeared to cause a sharp upswing in weight and a lesser upturn in the height age line.

In 1940-1941 both patients were given identical treatment with antuitrin growth according to the "special" method described. It is of interest to note the sharp upswing of J. N.'s curve which converged on J. R.'s curve and probably would have passed it had treatment been continued. J. N. is again under treatment with J. R. now acting as control. Further results of treatment of this interesting pair will be published later.

Case 4.—G. B., admitted at the age of 10 years (1935); white boy of American parentage, father's ascendants French-Canadian; parents mentally and socially low average. Normal birth; pneumonia when 1 year old, followed by "sleeping sickness"; usual childhood diseases. At 4 years of age described as "a little living skeleton"; two serious head accidents when 6 and 7 years old.

Medical Examination.—Growth retardation; undernourished and undersized; roentgen examination (1937)—chronological age, 12 years; bone age, 6 years.

Psychologic Data.—Mental age, 6 years; I.Q., 60.

Diagnosis.—Mental deficiency (brain injury type); possible pituitary and thyroid dwarfism.

Treatment.—Because of several years delay in bone age as compared to chronological age, G. B. was regarded as mixed type endocrine deficiency with thyroid deficiency predominating. His growth is graphically portrayed in Fig. 5 (Curve IV). Between the ages of 10¼ and 12 years (123 to 144 on the ordinate of Fig. 5) he was untreated and his height quotient was practically stationary, below 60 per cent of normal. Between the ages of 12 and 13½ years he had thyroid in adequate dosage with some elevation of height quotient to 62 per cent. Between 13½ and

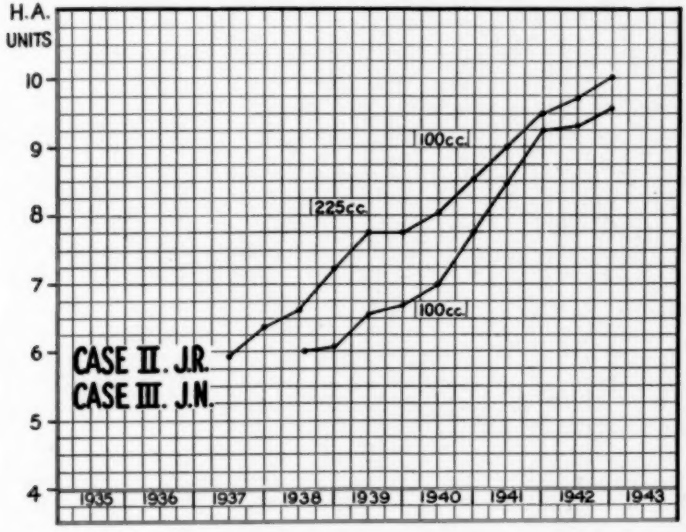

Fig. 3.—Height age curves of the two boys, J. R., and J. N., whose cases are discussed in this article. The top curve is of J. R. and is discussed in the legend for Fig. 2. J. N., who served as a control for J. R., was treated at the same time that J. R. received his second course of growth hormone. The number and interval of injections were the same in the two boys, as was the total amount of hormone given, 100 c.c. The upturn in J. N.'s height age line under treatment appears unmistakable.

14½ years she received antuitrin growth, 3 c.c., three times per week, with a rise in the height quotient to nearly 70 per cent. Treatment was discontinued for six months with a very clear sag in the curve of height quotient. The latter again rose when growth hormone was resumed and continued during G. B.'s fifteenth year. As noted above, we cannot attribute this boy's growth spurts to hormone therapy because of his age. It is perhaps significant, however, that growth spurts coincided with such therapy. It has not been shown, to our knowledge, that growth hormone therapy may not further accelerate the normal prepubertal growth spurt.

Comment.—The data concerning the height growth of these four patients have been treated according to Olson's method of recording by age units. Figs. 1 and 2 give the graphic representation of the

curves of the children in Cases 1 and 2. The two curves for height growth show clearly that the growth curve becomes divergent from the line presenting chronological age in the case of retardation or deceleration of growth. When growth hormone treatment was initiated, the height curve became convergent or ran parallel to the line representing life age. By this simple method of plotting growth (in height) in age units and comparing the height curve with the chronological age line it became possible to demonstrate the effectiveness of growth hormone therapy; the height curve which, before therapy, was divergent, under therapy became modified to change to a convergent or parallel course in respect to the life age line.

The same method can be used to compare two individuals if one is using matched pairs of children, treating one and leaving the other untreated. Fig. 3 shows the height curves of the children in Cases 2 and 3. The child in Case 2 was treated twice, the one in Case 3 only once (at the time of the second treatment of the child in Case 2). The height curve of the child in Case 3 became divergent to that of the one in Case 2 in the beginning and later convergent and parallel under treatment.

It is possible to employ a second method of recording increments in height growth when using the age unit method. Our children were measured every six months in height; one could record the increase in height age by months for each measured period. Fig. 4 presents all four cases recorded by this method. We have added the fourth case for demonstration. We are not so sure that this increase in height was only due to the treatment, because therapy was started during the adolescent period when changes in height growth are expected to occur physiologically. By this type of recording one sees that retardation of growth in height may appear as an age value less than 6 months (height age) during the time interval of measurements taken (6 months chronological age), and the influence of the therapy becomes evident by age values exceeding 6.

By using the age unit method a third approach of recording is possible. In the same manner as the intelligence quotient is derived by the ratio of mental age to chronological age, one can obtain a height quotient by dividing actual height age by chronological age. In plotting the obtained height quotients of a given case on graph paper, one draws a curve in which the modification produced by therapy is shown in an increase in height quotient. Fig. 5 shows this type of recording for the children in our four cases.

Summary and Discussion.—It is emphasized that there is a need for accurate recording of growth changes when the effectiveness of growth hormone therapy or other forms of treatment are investigated. The evaluation of a given therapy depends on the degree of modification appearing in growth. The age unit method[4] appears to be a satisfactory and simple method of recording growth.

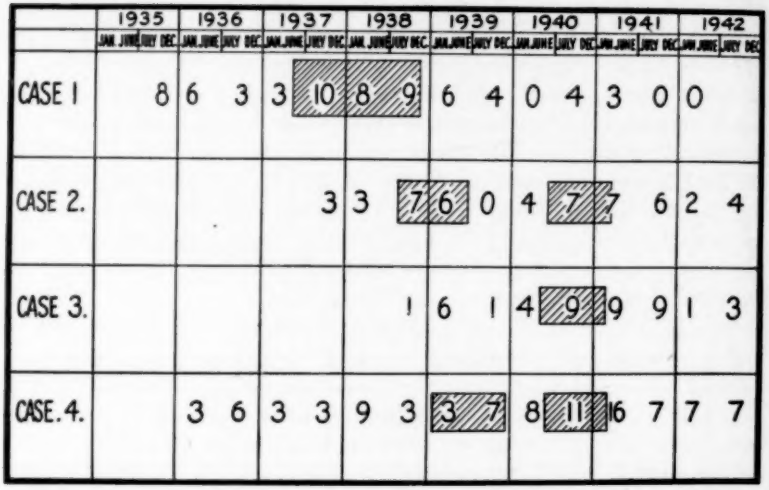

Fig. 4.—Increments in growth may be recorded in age units. Our study measurements made at six-month intervals are used for recording; therefore, the figure 6 appearing in the above illustration indicates a normal increase in height during the six-month period represented; figures less or greater than 6 represent height increments correspondingly less or greater than the expected normal. When we tabulate the height growth of the four patients here reported, it is noted that height increments greater than those expected are significantly associated with growth hormone therapy (the shaded blocks represent treatment with antuitrin growth). This is particularly true of the children in Cases 1, 2, and 3. No conclusions can be drawn from Case 4 because of his age when treated.

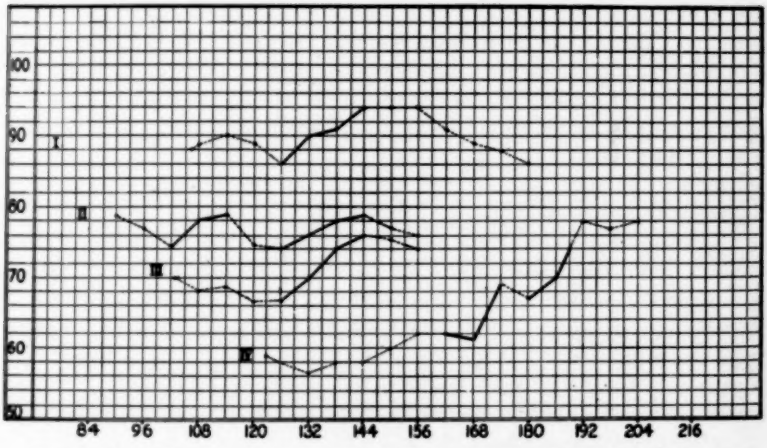

Fig. 5.—In addition to the two methods of tabulating growth increments in terms of age units, illustrated in Figs. 1 to 4 inclusive, still a third method of presenting data may be derived from age unit figures. Corresponding to the method of determining intelligence quotient (I.Q.), a height quotient may be obtained by dividing height age by chronological age. The values as obtained (percentages) may be plotted on graph paper to indicate the trend of the patient's height growth. When this is done for our four patients and the periods of growth hormone administration shown by heavy portions of the curves, the influence of growth hormone on the height age and height quotient is very apparent.

Three ways of demonstrating growth increments are presented:

1. A method which by inspection readily indicates whether there is divergence, parallelism, or convergence of the subject's height curve as compared to the line representing chronological age. Retardation of growth shows itself by divergence; acceleration of growth, by convergence; and rate of growth at the speed of the normal individual, by parallelism.

2. In tabulating the increment in height age (in months values) over regular six-month periods, values over 6 represent acceleration and under 6 retardation in growth, respectively.

3. By using a height ratio (height quotient) statistical data can be obtained showing the degree of modification more accurately.

This preliminary report attempts to clarify terms and methods with respect to measurement and statistical evaluation of growth rather than to demonstrate and evaluate the effectiveness of pituitary growth hormone therapy. It has been shown, however, in Cases 1, 2, and 3 that the subjects' height curves became convergent while on (and for a period following) growth hormone therapy, and that the same curve tended to be divergent before and after hormone treatment. In a subsequent paper the clinical differentiation of pathologic growth in mentally defective children and the modification of growth which can be produced by specific hormone therapy will be presented.

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PROTECTION OF THE INFANT AGAINST DIPHTHERIA DURING THE FIRST YEAR OF LIFE FOLLOWING THE ACTIVE IMMUNIZATION OF THE PREGNANT MOTHER

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INTRODUCTION

THE occurrence of diphtheria antitoxin in the blood serum of the human pregnant mother and newborn infant and in the placenta and colostrum was presented in previous articles.[1, 2] It is the purpose of this publication to present additional findings on the nonimmunized and actively immunized mothers and to relate what effect such immunization had upon the infant during the first year of life.

It had been planned to obtain small amounts of blood from the infants at spaced intervals to determine the changes in the diphtheria antitoxin level during the first year of life. In a number of infants this plan was carried as far as the third month of life, when it was found impractical to continue further. Consequently, the Schick test was substituted as a means to obtain significant information.

METHODS

Diphtheria antitoxin titers were determined on both mothers and infants at six weeks and three months following birth of the infant. Blood for these determinations was obtained from the cubital vein of the mother and by heel puncture of the infant. Antitoxin titers were ascertained by the intracutaneous test in rabbits, using the Moss-Jones modification of the method reported by Fraser.[3*] Schick tests were done in the usual manner, using diphtheria toxin prepared by the Biological Laboratory of the Illinois Department of Public Health.

The difficulties involved in investigational work of this type, which requires the following of clinic patients over a period of time, is best appreciated by those who have attempted such a problem.

RESULTS

Nonimmunized Schick-Positive Mothers.—Nonimmunized Schick-positive mothers with an original antitoxin titer of 0.002 units or less per milliliter of serum showed no rise in the titer level at parturition and failed to show any changes at six weeks, three months, and six months following birth of the infant (Table I).

From the Department of Obstetrics, St. Vincent's Hospital, and the Department of Bacteriology, Northwestern University Medical School.

*These tests were carried out by Eli Lilly and Company Research Laboratories.

The infants born to these nonimmunized Schick-positive mothers possessed at birth a diphtheria antitoxin level equal to that of the mothers—0.002 units per milliliter of serum—and showed no change in this titer level at six weeks, three months, and six months of age (Table I).

The Schick tests of these infants at birth, except Case 32, were positive and remained positive during the first year of life (Table I).

TABLE I

DIPHTHERIA ANTITOXIN LEVELS IN NONIMMUNIZED SCHICK-POSITIVE MOTHERS AND THEIR OFFSPRING AND SCHICK TESTS ON THESE OFFSPRING FOLLOWED ONE YEAR FROM THE TIME OF DELIVERY

ANTITOXIN LEVELS IN MOTHERS					ANTITOXIN LEVELS IN OFFSPRING				SCHICK TEST ON OFFSPRING		
ORIGINAL TITER LEVEL, 0.002 UNITS PER MIL. OF SERUM OR LESS											
CASE	AT TERM	6 WK. AFTER BIRTH	3 MON. AFTER BIRTH	6 MON. AFTER BIRTH	AT BIRTH	AT 6 WK.	AT 3 MON.	AT 6 MON.	AT BIRTH	AT 6 MON.	AT 1 YR.
6	0.002	0.002		0.002	0.002	0.002		0.002	+		+
7	0.002	0.002	0.002		0.002		0.002		+		+
16	0.002	0.002		0.002	0.002		0.002		+	+	
19	0.002	0.002	0.002		0.002		0.002		+		+
20	2.0			1.0							
21	0.002		0.002	0.002	0.002		0.002	0.002	+	+	
32	0.002	0.002		0.002	0.002		0.002		−	+	
48	0.002	0.002		0.002	0.002	0.002	0.002		+		+

Antitoxin titer expressed in units per milliliter of blood serum.

TABLE II

DIPHTHERIA ANTITOXIN LEVELS IN NONIMMUNIZED SCHICK-NEGATIVE MOTHERS AND THEIR OFFSPRING AND SCHICK TESTS ON THESE OFFSPRING FOLLOWED ONE YEAR FROM THE TIME OF DELIVERY

ANTITOXIN LEVELS IN MOTHERS					ANTITOXIN LEVELS IN OFFSPRING				SCHICK TEST ON OFFSPRING		
ORIGINAL TITER LEVEL > 0.002 MIL. UNITS PER C.C. OF SERUM											
CASE	AT TERM	6 WK. AFTER BIRTH	3 MON. AFTER BIRTH	6 MON. AFTER BIRTH	AT BIRTH	AT 6 WK.	AT 3 MON.	AT 6 MON.	AT BIRTH	AT 6 MON.	AT 1 YR.
5	0.2	0.2		0.2	1.0		0.1				
8	1.0	2.0	2.0								
9	1.0	1.0		1.0							
12	2.0	2.0			2.0		0.1		−	−	+
13	0.002	0.5		0.5	1.0	0.2		0.1	−	−	−
20	0.1	10.0	0.1		10.0	0.2	1.0		−	−	−
35	2.0			2.0	2.0			5.0	−		+
40	1.0	2.0			2.0	0.5		0.5	−	−	+
45					0.5	0.5			−	−	
46	1.0	2.0	1.0		2.0		0.1		−	−	
50	0.1			0.5	0.1		0.1		−		−
52	1.0		0.5		2.0			2.0	−	−	

Nonimmunized Schick-Negative Mothers.—Nonimmunized Schick-negative mothers with titers greater than 0.002 units per milliliter of serum at the time of parturition showed, in most instances, no change in the antitoxin level at six weeks and three months after the birth of

the infant. The patients in Cases 13 and 50 of this group showed an increase over the antitoxin titer level at parturition.

Infants born to this group of mothers had at birth, in most instances, an antitoxin level equal to that of the mothers at term. A decline in the diphtheria antitoxin level was observed in this group of infants watched over a period of six months, but in none did the antitoxin level fall below that of Schick immunity (Table II).

Schick tests on the offspring of the nonimmunized Schick-negative mothers were negative at birth. All of the infants in this group were still Schick negative at 7 to 10 months of age. Some infants presented negative Schick tests at 13 months of age (Cases 13 and 20, Table II), whereas others who had previously had negative Schick tests became Schick positive at the end of the first year of life (Table II).

TABLE III

DIPHTHERIA ANTITOXIN LEVELS IN ACTIVELY IMMUNIZED SCHICK-POSITIVE MOTHERS AND THEIR OFFSPRING AND SCHICK TESTS ON THESE OFFSPRING FOLLOWED ONE YEAR FROM THE TIME OF DELIVERY

ANTITOXIN LEVELS IN MOTHERS					ANTITOXIN LEVELS IN OFFSPRING				SCHICK TEST ON OFFSPRING		
	ORIGINAL TITER LEVEL, 0.002 UNITS PER MIL. OF SERUM OR LESS										
CASE	AT TERM	6 WK. AFTER BIRTH	3 MON. AFTER BIRTH	6 MON. AFTER BIRTH	AT BIRTH	AT 6 WK.	AT 3 MON.	AT 6 MON.	AT BIRTH	AT 6 MON.	AT 1 YR.
10	5.0	5.0	5.0								
15	0.2	0.2	0.2		0.2	0.002			–	–	
17	0.01	0.05			0.01	0.005	0.002		–	–	
23	0.5		1.0		0.002		0.2				
25	0.002	0.1			0.002	0.002			–		+
32	0.2	0.2		0.2							
36	5.0	10.0			10.0	5.0			–	–	
37	5.0		5.0		5.0	2.0		1.0	–	–	–
44	0.002	0.05			0.002	0.002			–	+	
49	0.02		0.1		0.2	0.002			–	+	
53	0.1	0.1		0.1	0.2		0.1		–	–	

Actively Immunized Schick-Positive Mothers.—Schick-positive mothers subsequently actively immunized showed in most cases a rise in the diphtheria antitoxin level at parturition (Table III). In spite of successful active immunization, the patients in Cases 25 and 44 (Table III) showed no rise in the titer level at this time. Six weeks post-partum there was an increase in the titer value of the patients in these two cases. In the remainder of the patients the titer value was either slightly increased or remained the same at six weeks and three months following the birth of the offspring. In one instance the antitoxin level remained up as long as six months.

Infants born to actively immunized Schick-positive mothers had an antitoxin level, in nearly all cases, equal to that of the mothers at parturition (Table III). At 6 weeks of age the titer value was diminished in all but two infants (Cases 25 and 44, Table III). These two infants

failed to show any appreciable antitoxin at birth. The infant in Case 23, on the other hand, showed at 3 months a rather marked increase in the antitoxin value over that which was found at birth.

The offspring of these actively immunized Schick-positive mothers were Schick negative at birth. Some of these remained Schick negative at 7 and 13 months of age; others became positive at 9 months to 1 year (Table III). Although the antitoxin titers of the infants in Cases 25 and 44 are below the level of Schick immunity, the skin tests in both cases were negative at birth.

Actively Immunized Schick-Negative Mothers.—Schick-negative mothers who were actively immunized all showed a marked rise in the diphtheria antitoxin level at parturition. In nearly all the patients this level did not change three months after the birth of the offspring and continued to be high or unchanged at the end of from six to ten months. (Table IV).

TABLE IV

DIPHTHERIA ANTITOXIN LEVELS IN ACTIVELY IMMUNIZED SCHICK-NEGATIVE MOTHERS AND THEIR OFFSPRING AND SCHICK TESTS ON THESE OFFSPRING FOLLOWED ONE YEAR FROM THE TIME OF DELIVERY

ANTITOXIN LEVELS IN MOTHERS					ANTITOXIN LEVELS IN OFFSPRING				SCHICK TEST ON OFFSPRING		
ORIGINAL TITER LEVEL > 0.002 C.C. UNITS PER MIL. OF SERUM											
CASE	AT TERM	6 WK. AFTER BIRTH	3 MON. AFTER BIRTH	6 MON. AFTER BIRTH	AT BIRTH	AT 6 WK.	AT 3 MON.	AT 6 MON.	AT BIRTH	AFTER 6 MON.	AFTER 1 YR.
1	50.0	20.0	10.0								
4	10.0	10.0	5.0	5.0	20.0		2.0	2.0	–	–	
11	20.0	10.0	20.0	10.0	20.0	10.0		2.0	–	–	–
18	20.0		20.0		50.0		20.0	10.0	–	–	–
22	5.0				5.0				–		–
27	5.0				10.0				–	–	
29	20.0				50.0				–		–
39	5.0	5.0	5.0		5.0	2.0			–	–	+
41	50.0			20.0	50.0			2.0	–	–	
43	10.0	10.0			20.0		5.0		–	–	–
54	50.0		20.0	20.0	100.0			10.0	–	–	
59	10.0		5.0		10.0		2.0		–		–
62	10.0			5.0	10.0		2.0		–		–

Infants born to this group of mothers had, in the majority of cases, an antitoxin level equal to that of the mothers at term. Most infants at three and six months of age showed a marked decrease in the antitoxin titer when compared to the level present in the blood serum at birth, whereas others showed decreases of lesser degree. In no infant at 6 months of age was the antitoxin titer reduced to that of the mother before immunization was instituted.

Schick tests on the offspring of this group of actively immunized Schick-negative mothers were negative at birth and remained negative as late as 15 months of age. The infant in Case 39 (Table IV) is the only exception to this statement, inasmuch as the Schick test became positive at 12 months.

DISCUSSION

The majority of investigators dealing with the placental transfer of passive immunity to the offspring have concluded that such protection persists about six months. Later an active immunity is acquired in the majority of instances either by having the disease or by subclinical exposure.

Schick,[4] reporting on a large number of individuals of varying age groups, found that 16 per cent of the newborn infants were Schick positive, and thus susceptible to diphtheria shortly after birth, over one-half are Schick positive at 6 months of age and from 80 to 90 per cent of infants possess a positive Schick test at the end of the first year of life.

Greengard and Bernstein[5] have shown that active immunization against diphtheria in the very young infant, 3 to 6 months in age, does not result in an effective protection. He has demonstrated that the Schick tests of infants actively immunized at 6 months of age are more likely to become positive than those of a similar group of infants immunized after the eighth month of life.

Freund,[6] reporting the influence of age upon antibody formation, found that rabbits less than 20 days af age formed agglutinins, hemolysins, and precipitins very poorly as compared with adult rabbits.

Although the number of cases followed through in this study was small, the results reported in this communication revealed that the active immunization of the pregnant mother will provide by the passive transfer of immune bodies a prolonged protection of the infant during the period of least resistance. The importance of this extended passive immunity during the first year of life of the infant is conveyed by results such as those of Greengard. The duration of the passive immunity thus produced will, as pointed out by Neill, Gaspari, Richardson, and Sugg,[7] be a function of two factors: (a) the amount of antitoxin originally received and (b) the rate of its loss from the body. These facts are well demonstrated by the findings in Tables III and IV. The results further show that the amount originally transferred from the mother to the infant need not be excessive to produce sufficient passive protection. As little as 0.01 unit of antitoxin per milliliter of blood serum of the infant at birth was sufficient in protecting through the first six months of life. This thus enables the offspring to be carried through the period of greatest susceptibility and up to the age whence active immunization may be instituted with the greatest benefit resulting therefrom.

The decrease in immune bodies, in terms of units of antitoxin per milliliter of blood serum, in Schick-positive and Schick negative mothers actively immunized compared with a similar decline of the passive immune bodies of the respective infants is demonstrated by Tables III and IV. The diphtheria antitoxin level in the actively immunized mothers remained high as late as six months after the birth of the off-

spring. In fact, some mothers of the infants in the actively immunized Schick-positive group continued to show an increase in the titer level. This occurred six or seven months following the initial toxoid injection. This is not unusual, as it is believed by many that complete response to active immunization requires from three to six months. It is, however, an exception to the findings previously reported,[1] which indicated maximum response to toxoid immunization in from four to eight weeks. The decline in the passive immune bodies of the respective offspring (Tables III and IV) is, however, two to five times greater than in the mothers.

The height of antibody response as indicated by the findings in Tables III and IV, demonstrates the principals of primary and secondary antigenic stimuli as discussed by Glenny and Allen.[8] Nonimmunized mothers with an antitoxin level above that of Schick immunity (Table II) responded sufficiently to the use of the Schick material to produce an elevation of the titer level. This persisted, and the transplacental transfer of the immune bodies to the offspring was sufficient to protect the infants through the first year of life. This is confirmed by the results of Schick tests on this group (Table II). As a result of these findings, it is safe to assume that a Schick test performed as a routine procedure upon the pregnant mother would have a twofold purpose: (a) it would demonstrate and separate the negative mother from the positive and (b) at the same time it would serve as a secondary stimulus to the already Schick-negative mother. The Schick-positive mothers, on the other hand, would require active immunization.

Schick tests performed on infants at 6 weeks and 6 months of age did not act as secondary stimuli to the already Schick-immune infants, as the infants previously Schick negative (Tables II, III and IV) turned positive in a number of instances. Those who remained negative after the first year of life had, in most instances, a high antitoxin, titer at birth which undoubtedly was prolonged. This failure to respond to Schick test material may be explained on the basis that in the presence of passive immunity no production of antitoxin results because of overneutralization of the mixture[9] or that antibody formation fails to occur in the very young because of an immature reticuloendothelial system.

Although diphtheria is not a frequent disease of infants during the first year of life, the above findings are further confirmatory evidence as to the protective value afforded the offspring from the active immunization of the pregnant mother. This increased and extended passive immunity serves the infant during the time when active immunization of itself would not result in 100 per cent protection of those infants.

In view of these encouraging results, it is our intention to do a similar series of cases in an attempt to protect the offspring against whooping cough, a disease most prevalent in the first year of life, when the highest morbidity and mortality rates occur.

CONCLUSIONS

1. Active immunization of the pregnant mother results in an increased placental transfer of passive immune bodies to the offspring.

2. The increase in passive immune bodies to the offspring is prolonged sufficiently to increase the protection during the first year of life.

3. Schick tests on pregnant mothers immune to diphtheria acted as a secondary antigenic stimuli, causing increased antitoxin formation. This was sufficient to prolong the passive immunity in the offspring of this group of mothers.

4. Schick tests on infants immune to diphtheria did not increase their antitoxin titers.

5. The decline of passive immune bodies in the offspring is two to five times greater than the decline of active immune bodies in the respective mothers.

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AN EVALUATION OF THE BLOOD AND URINARY THIAMINE DETERMINATIONS IN VITAMIN B_1 SUBNUTRITION

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VITAMIN B_1 subnutrition is believed to be sufficiently common to warrant serious attention not only by students of nutrition, but also by all practicing physicians. These subnutritional cases, however, are difficult to recognize for they are not revealed by obvious signs or precise symptoms. Such symptoms as lassitude, anorexia, and mental depression have been reported[1] in patients who were on restricted diets, but a definite diagnosis of thiamine deficiency cannot be made on the basis of these tenuous symptoms. Laboratory procedures, therefore, are required for the detection and study of vitamin B_1 subnutritional states.

We have reported[2] on the urinary thiamine excretion of "healthy" children who were hospitalized and so could be kept under close observation. We learned that a child with thiamine tissue saturation will present the following findings: (1) A daily intake of more than 900 μg (300 I.U.) of thiamine and a thiamine-calorie ration of 400 μg per 1,000 calories; (2) an average of 150 μg or more of thiamine is excreted daily in the urine; (3) 20 per cent or more of the ingested thiamine is excreted in the urine.

The urinary thiamine excretion of seventy-five ill children (acute, chronic, and convalescent conditions) was then studied.[3] The children with common colds (simple coryza) excreted 25 per cent or more of the dietary thiamine intake, but in all the other patients with acute and early convalescent conditions there was less than 20 per cent excretion of the ingested thiamine. Among the children with chronic conditions there were wide variations in the thiamine outputs and in the percentages of the intake which were excreted; some excreted well over 100 μg and 20 per cent of the intake, while others excreted appreciably less.

Fifty-five children[3] received test doses in an attempt to find a suitable saturation test. Theoretically, if the tissue reservoir is not saturated, a smaller fraction of the injected thiamine should be eliminated in a standard limit of time. Such a procedure would be a valuable function test for vitamin B_1 deficiency. In our patients with slight tissue unsaturation (vitamin B_1 subnutrition), the test dose results were so variable and inconsistent that they were of no value, but this does not rule out the possibility that test doses may be of value in

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verifying actual clinical deficiency states. In vitamin B_1 subnutritional states we felt that the most valuable information was obtained by determining the percentage of an adequate dietary thiamine intake which was excreted in the urine. This really constitutes the best test dose as there are no artificial conditions imposed.

On the basis of these urinary thiamine studies we learned that a child with vitamin B_1 subnutrition will fail in varying degrees to meet one or more of the three fold requirements of thiamine tissue saturation. These requirements are: (1) a daily intake of more than 900 μg (300 I.U.) of thiamine and a thiamine-calorie ratio of 400 μg per 1,000 calories; (2) an average of 150 μg. or more of thiamine is excreted in the urine; (3) 20 per cent or more of the ingested thiamine is excreted in the urine. A child may be moderately low on any one of these three requirements without having definite tissue unsaturation, but if he fails, even slightly, to meet two or more of these essential values, it is safe to conclude that his tissues are not saturated with thiamine. Calculation of the output:intake percentage is of greatest value in those children whose thiamine intake, during the study period, approaches normal and whose excretion values are only moderately lowered, a percentage of less than 20 per cent signifying thiamine tissue unsaturation. When both the thiamine intake and excretion values are markedly decreased, there is no need to compute the output:intake percentage in order to evaluate the state of vitamin B_1 nutrition. A marked decrease in any one of the three requirements is always accompanied by a significant lowering of the other findings and always signifies tissue unsaturation. Thus a daily intake of less than 600 μg, an average excretion of less than 100 μg, or the excretion of less than 16 per cent of the ingested thiamine, invariably denotes thiamine tissue unsaturation,

We feel that these excretion studies reflect the degree of thiamine tissue saturation of the body and assure the detection of patients with vitamin B_1 subnutrition. This method, however, requires painstaking collection of twenty-four-hour urine specimens for several days and also detailed computation of dietary thiamine intake. Methods of determining the vitamin B_1 blood levels were available and presented the possibility of a less arduous procedure for eliciting tissue unsaturation levels. It, therefore, seemed profitable to study the relationship of the blood vitamin B_1 to the urinary thiamine excretion.

It was necessary to ascertain the range of thiamine blood levels in normal children before attempting to evaluate the use of blood determinations as a possible function test in vitamin B_1 subnutrition. The forty-five children used in this study[4] were hospitalized and so could be kept under close observation. Complete histories were taken and physical and laboratory examinations were made to determine whether the child was clinically healthy. The urinary thiamine excretion in relation to the dietary thiamine intake was estimated for each child

to ascertain thiamine tissue saturation. Since each child ingested approximately 990 μg of thiamine, excreted over 150 μg of thiamine, and excreted over 20 per cent of the dietary thiamine intake, we deduced that these subjects had thiamine tissue saturation. During the week of thiamine excretion studies, we performed four prebreakfast blood determinations on each individual. An accurate thiochrome method,[5] which determines the total vitamin B_1 content of the blood, was used. In these healthy children, the blood level of vitamin B_1 ranged from 4.8 to 12.3 μg with a mean of 7.8 ± 1.3 μg.

With this knowledge of the range of vitamin B_1 blood levels in healthy children we were able to proceed with a study of vitamin B_1 blood levels in ill children. Children in the wards of Metropolitan Hospital, who might possibly have had vitamin B_1 subnutrition, were chosen for this investigation. They were selected if they presented any one or all of the following criteria: (1) History of a poor diet or suggestive symptoms such as anorexia, lassitude, etc., (2) appearance of malnutrition, (3) presence or history of a prolonged febrile disease. Each child received a careful study including history, physical examination, and indicated laboratory procedures. The daily dietary intake of carbohydrate, protein, fat, total calories, and thiamine was computed. The daily urinary thiamine excretion was measured during an entire week, and the percentage excretion of dietary thiamine was calculated. During this week each individual had four prebreakfast blood determinations for vitamin B_1. We used the same thiochrome methods for urine[6] and blood[5] determinations in this study that were utilized for our previously reported data.

TABLE I

	NUMBER OF PATIENTS	THIAMINE INTAKE (μg)	THIAMINE EXCRETION (μg)	INTAKE EXCRETED (%)	THIAMINE BLOOD VALUES (μg PER 100 C.C.)		
					LOW	HIGH	MEAN
Previously reported normal group[4]	45	800 to 1,100	All over 150	All over 20	4.8	12.3	7.8 ± 1.3
Group I	55	800 to 1,080	All over 150	20 to 47	5.0	13.7	8.2 ± 1.0
Group II	29	600 to 900	100 to 150	15 to 22	5.2	12.4	8.3 ± 1.0
Group III	15	500 to 700	70 to 100	10 to 17	4.5	10.7	8.0 ± 1.3
Group IV	22	243 to 600	23 to 69	5 to 15	5.5	13.9	8.0 ± 1.1

RESULTS

One hundred and twenty-one children suspected of having vitamin B_1 subnutrition were investigated, and on the basis of the urinary thiamine excretion studies they may be classified into four different groups (see Table I). Group I includes fifty-five children who meet the three requirements of thiamine tissue saturation: (1) Thiamine intake of more than 900 μg, (2) thiamine excretion of over 150 μg, and (3) excretion of at least 20 per cent of the ingested thiamine. There were no cases of pneumonia, active rheumatic heart disease, or any other

severe illness in the children in this group. The range of blood thiamine levels in the children in this group was from 5.0 to 13.7 μg with a mean of 8.2 ± 1.0 μg.

Group II consists of twenty-nine children whose levels are slightly below the ideal values, and these children may be considered as being on the borderline as regards their vitamin B_1 nutrition. The children in this group have a thiamine intake of from 600 to 900 μg, an average urinary thiamine excretion of from 100 to 150 μg, and from 15 to 20 per cent excretion of the ingested thiamine. Patients with mild acute infection, infantile eczema, inactive rheumatic heart disease, acute bronchitis, and two children with lobar pneumonia are included in this group. The range of blood thiamine levels was from 5.2 to 12.4 μg with a mean of 8.3 ± 1.0.

Group III consists of fifteen children whose levels are definitely below normal values; thiamine intake of from 500 to 700 μg, thiamine excretion of from 70 to 100 μg, and from 10 to 17 per cent excretion of the ingested thiamine. This group includes seven patients with pneumonia, two with active rheumatic heart disease, and six with severe cases of acute sinusitis, tonsillitis, and otitis media. The range of blood thiamine levels was from 4.5 to 10.7 μg with a mean of 8.0 ± 1.3.

Group IV consists of twenty-two children who definitely have thiamine tissue unsaturation as reflected by markedly low values; thiamine intake of from 243 to 600 μg; thiamine excretion of from 23 to 69 μg, and only from 5 to 15 per cent excretion of the ingested thiamine. This group includes patients with kidney disease, ulcerative colitis, hyperthyroidism, and severe febrile infections with accompanying symptoms of marked anorexia, vomiting, or diarrhea. The range of blood thiamine levels was from 5.5 to 13.9 μg with a mean of 8.0 ± 1.1.

Since the twenty-two children in the last group are definite examples of thiamine tissue unsaturation, they merit more detailed attention and are listed in Table II. The values of thiamine intake, excretion, output:intake percentage, and average vitamin B_1 blood levels are recorded for each individual (the children vary between 2½ and 11 years of age). Accompanying the diagnosis are the clinical data that have a significant bearing on the production of thiamine tissue unsaturation, and it may be noted that most of these children had symptoms of vomiting, diarrhea, or anorexia in addition to a severe illness. In spite of the unequivocal evidence of thiamine tissue unsaturation as shown by the urinary excretion studies, the average vitamin B_1 blood level of each child is within the same range of values as the group of normal children previously reported.

COMMENTS

These studies were undertaken in the hope that determinations of the vitamin B_1 blood levels would provide a comparatively simple procedure for eliciting varying degrees of thiamine tissue unsaturation.

TABLE II

DATA ON CHILDREN WITH DEFINITE VITAMIN B_1 SUBNUTRITION (GROUP IV)

CASE	AVERAGE B_1 INTAKE (μg)	AVERAGE B_1 OUTPUT (μg)	B_1 OUTPUT B_1 INTAKE (PER CENT)	AVERAGE B_1 BLOOD LEVELS (μg)	DIAGNOSIS	CLINICAL MANIFESTATIONS
1	540	30	6	7.2	Acute hemorrhagic nephritis	History of sore throat with temperature of 102° F. for week; vomiting for first two days in hospital; classical findings of acute nephritis
2	570	58	10	8.9	Pyelonephritis	7 years old; weight, 43 pounds; previous admissions for pyelonephritis associated with ureteral anomaly; present admission with fever 105° F., chills, vomiting, and cloudy urine; appetite poor for several months
3	552	40	7	6.8	Chronic ulcerative colitis	10 years old; weight, 50 pounds; frequent loose bloody, mucous stools; had been having such episodes for past five years
4	639	47	7	9.5	Malnutrition and acute tonsillitis	11 years old; weight, 62 pounds; child had a fistula following mastoid operation several year previously; appetite said to be poor; admitted for tonsillitis with fever of 104° F. and loose watery stools
5	744	55	7	8.0	Active rheumatic heart disease	Admitted with joint pains and sedimentation rate 50/125 but no cardiac lesion; within ten days after admission there was a double mitral murmur and questionable aortic lesion; child was critically ill and toxic
6	711	50	7	9.8	Influenza	Recurrent attacks of abdominal pain for a month prior to admission, with occasional episodes of vomiting; appetite poor for a month; temperature of from 101 to 103° F. for three days after admission
7	531	41	8	8.1	Tuberculous cervical and hilar adenopathy	Large doughy cervical glands; 4 plus Mantoux test; appetite poor for several weeks prior to admission; low-grade fever; rapid sedimentation rate

TABLE II—CONT'D

CASE	AVERAGE B_1 INTAKE (μg)	AVERAGE B_1 OUTPUT (μg)	B_1 OUTPUT B_1 INTAKE (PER CENT)	AVERAGE B_1 BLOOD LEVELS (μg)	DIAGNOSIS	CLINICAL MANIFESTATIONS
8	657	54	8	8.5	Acute stomatitis	Fever for six days with sores in the mouth; refused any food, even fruit juices for several days prior to admission
9	600	55	9	9.9	Acute pharyngitis following T. & A.	T. & A. performed two weeks prior to this admission; parents state child had lost ten pounds; appetite very poor; child also had congenital syphilis
10	498	49	10	7.3	Acute Tonsillitis	Vomited everything taken by mouth for three days prior to admission; temperature of 103° F. for several days
11	636	68	11	9.8	Sinusitis bronchiectasis	9 years old; weight, 50 pounds; ill for six months prior to admission, with cough and low-grade fever; appetite very poor; mother stated child lost five pounds in previous six months
12	640	68	11	9.1	Acute pharyngitis	Fever, 102 to 104° F. for three days; did not eat anything but drank orange juice and vomited several times for two days prior to admission; history of acute rheumatic fever one month before admission
13	633	63	10	6.9	Peritonsillar abscess	Ill for five weeks with temperature of from 100 to 102° F.; appetite very poor and child took hardly any food for last week prior to admission; fever of from 102 to 104° F. for five days after admission
14	502	23	5	7.7	Acute laryngitis	2½ years old; weight, 28 pounds; appetite poor since birth; history of frequent episodes of croupy cough for eight months; allergic to eggs
15	569	61	11	7.8	Pneumonia of right upper and lower left lobes	Temperature of from 102 to 104° F. for four days; vomiting and loose stools prior to admission; child very toxic

TABLE II—CONT'D

CASE	AVERAGE B_1 INTAKE (μg)	AVERAGE B_1 OUTPUT (μg)	B_1 OUTPUT B_1 INTAKE (PER CENT)	AVERAGE B_1 BLOOD LEVELS (μg)	DIAGNOSIS	CLINICAL MANIFESTATIONS
16	483	53	11	8.6	Lobar pneumonia and acute purulent otitis media	5 years old; weight, 37 pounds; fever and vomiting for two days prior to admission; very toxic; temperature, 105.4° F.
17	480	59	12	6.3	Bronchopneumonia	Critically ill with fever of from 104 to 106° F. for seven days despite chemotherapy; oxygen tent required for five days; past history of asthma
18	465	54	12	8.2	Bronchopneumonia	Temperature of from 103 to 105° F. for three days; appetite poor; frequent vomiting
19	261	33	13*	6.9	Active rheumatic heart disease	11 years old; weight, 55 pounds; acute rheumatic pancarditis with stormy clinical course resulting in death a few months after admission
20	247	42	17*	6.3	Active rheumatic heart disease	8 years old; weight, 45 pounds; stormy course including several episodes of congestive failure
21	243	39	16*	8.7	Ruptured appendix and peritonitis	Poor appetite, abdominal pain, and fever for one week prior to admission; Wangensteen suction tube and Miller-Abbot tube used; intravenous fluids for five days postoperatively
22	361	52	14*	6.7	Toxic hyperthyroidism	7 years old; weight, 42 pounds; classical picture of thyrotoxicosis; B.M.R., plus 29; appetite poor; child losing weight

*Percentage calculation is erroneous when dietary intake is very low.

All of the 121 children, however, had vitamin B_1 blood levels that were within the same range as the values previously reported in a group of normal children, that is, a mean of 7.8 ± 1.3 μg, with a range of 4.8 to 12.3 μg. Even the twenty-two children (group IV) with unequivocal evidence of thiamine tissue unsaturation had blood levels that were within the normal range. We conclude, therefore, that determinations of thiamine blood levels are useless for the detection of vitamin B_1 subnutritional states; that is, thiamine tissue unsaturation without clinical signs or definite symptoms.

The work of other investigators substantiate this viewpoint. Pannekoek-Westenburg and van Veen[7] state that no conclusions as to the

presence of vitamin B_1 deficiency may be drawn merely from the aneurin (thiamine) level of the blood, and they believe that blood tests are of no practical importance. Youmans and co-authors[8] suggest from their results, "a fall in the blood thiamine level may not occur sufficiently in the progressive course of a deficiency state to make this determination valuable as a diagnostic aid in 'subclinical' thiamine deficiency." It seems reasonable, however, to expect the blood thiamine level to fall in instances of severe clinical thiamine deficiency, and this has been shown to occur. Youmans and co-authors[8] and Goodhart and co-authors[9, 10] have reported that most patients with peripheral neuritis have blood thiamine levels of 3.5 μg or less. Lehman and Nielsen[11] have presented a case of a patient who had Beriberi with a thiamine blood level of 1.0 μg which rose to 12 μg following the administration of vitamin B_1, and the patient maintained a level of 10 μg after recovery.

It may be postulated, therefore, that the amount of vitamin B_1 held in the blood apparently does not begin to fall until the stores of the vitamin in the tissues are almost exhausted and it is the state of the tissues that really tells the story. Urinary excretion studies reflect the degree of thiamine tissue saturation or unsaturation and are the best means, at present, for evaluating vitamin B_1 subnutritional states.

A detailed history will help to indicate those cases with vitamin B_1 subnutrition. The patient may present such vague complaints as loss of appetite, constipation, easy fatigue, and irritability. There should, however, be particular inquiry along the following lines:

1. Is there an adequate dietary intake of thiamine, about 450 μg per 1,000 calories?

2. Has absorption of vitamin B_1 been impaired by such factors as diarrhea and persistent vomiting?

3. Has there been an increased demand for thiamine because of increased metabolism as in hyperthyroidism and prolonged febrile diseases?

4. Has the urinary excretion been markedly increased and the thiamine washed out as in large intravenous infusions before and after operations?

There may be several of the above or similar factors leading to vitamin B_1 subnutrition in an individual.

At present, the diagnosis of vitamin B_1 subnutrition can only be confirmed by laboratory studies. The urinary excretion studies have proved satisfactory for this purpose. The individual to be studied is given a prescribed diet containing an adequate amount of thiamine (450 μg per 1,000 calories). This gives more accurate information than the test dose. The twenty-four-hour urine is collected on two succeeding days and the amount of thiamine determined. Then on the basis of the criteria given above, the diagnosis is confirmed or disproved. This study is not expensive to perform. In an equipped laboratory, the technician can do sixteen determinations a day.

Once diagnosis of vitamin B_1 subnutrition is made, the patient should be given vitamin supplements for at least two weeks. It is best to use the vitamin B complex in therapy, since there probably is an associated subnutrition of the other members of the B complex. The vitamin should be given in small divided doses rather than one large dose to obtain the maximum absorption. A careful education of the patient as to correct diet should be carried on before the patient is discharged. Particular emphasis is placed on the errors in the previous diet. This prophylaxis will assure the nonreturn of vitamin B_1 subnutrition and make it unnecessary to take vitamin supplements indefinitely.

CONCLUSIONS

1. The blood determination of thiamine is of no value in diagnosis of vitamin B_1 subnutrition.

2. Thiamine urinary excretion studies are useful for this purpose.

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THE COMPARATIVE EFFECTS OF AMMONIATED MERCURY, SULFATHIAZOLE, AND SOAP AND WATER ON THE SURFACE BACTERIA OF THE NEWBORN INFANT

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AN IDEAL routine of skin care for the newborn infant should keep him physically clean, be nonirritating, and prevent bacterial invasion of the skin. It is a question whether any of the routines in common use at the present fulfill all of these requirements. For the first requirement soap and water are adequate and easy, but these alone do not appear to be able to meet the last, as shown by the frequent epidemics of impetigo neonatorum recorded in the literature.[1] As an improvement, Chadwell, in 1928,[1] introduced the use of ammoniated mercury in conjunction with soap and water. Applications of ointments containing ammoniated mercury in strengths of from 2 to 5 per cent after the infant's first bath have been credited with reducing the incidence of impetigo neonatorum to a low figure.[1-3] A number of skin irritations have been reported associated with its use.[3, 4]

The recent successful use of sulfathiazole ointments in the treatment of skin lesions[5] suggested that this drug, applied to the newborn infant following the use of soap and water, might be as effective a prophylactic as ammoniated mercury, and preferable if free from irritating side effects.

The present report concerns primarily an attempt to compare, by means of skin cultures, the effects on the newborn infant's surface bacteria of ammoniated mercury and sulfathiazole ointments used in conjunction with soap and water, and of soap and water alone. Skin irritations and absorption of sulfathiazole are also considered.

METHOD

Healthy newborn infants, chosen at random from those delivered during the winter months of 1942 and 1943 on a private obstetric service, were the subjects. They were divided into three groups as follows:

Group I (thirteen infants): These infants were given an initial soap* and water bath from six to twelve hours after birth and immediately annointed once with an ointment containing 2½ per cent ammoniated mercury in a lanolin and petrolatum base.

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*The soap used in all cases was a liquid preparation known as "Baby San."

Group II (fourteen infants): These infants were given after the initial bath a single application of an ointment containing 7½ per cent sulfathiazole in a lanolin and petrolatum base.

Group III (fifteen infants): These infants were bathed with soap and water on the first, third, and fifth days of life but received no ointment.

The infants in Groups I and II were given a daily rubbing with sterile cottonseed oil after the first day of life. No more water was used on them other than a 1 per cent solution of boric acid for cleaning the diaper area.

The infants in Group III were rubbed with sterile cottonseed oil after each bath and on the intervening days.

All infants were housed in the same central nursery and were handled by the same group of nurses. During the time of this study there were no infections among the infants in the nursery serious enough to warrant isolation.

Skin cultures were taken in the following manner on all subjects: A drop of sterile broth culture medium was transferred to the skin and rubbed well over an area about 5 by 10 mm. by means of a sterile stiff wire loop. The loop was then lifted, and the adherent broth spread evenly over one-half of a blood agar plate. The plate was incubated at 37° C. for from eighteen to twenty-four hours, the organisms identified, and the amount of growth reported as "none," "few," "moderate," or "abundant." A more quantitative method of representing bacterial growth was felt to be unnecessary, due to the variables inherent in this method of sampling. The cultures obtained in this way were not expected to show all types of surface bacteria in their true numerical proportions but rather to favor the common pathogens.

The skin areas cultured were behind the ear, on the front of the neck, and in the groin. In addition, cultures were taken from the face on all infants in Group III.

In each group of infants the first set of cultures was taken following the initial bath (but before the application of an ointment when used), and subsequent sets were taken at twenty-four-hour intervals up to and including the fifth day of life.

Capillary blood sulfathiazole levels were taken at various intervals after application on eight of the infants in Group II. The skin puncture was made in an area to which the ointment had not been applied, since it was found that otherwise enough drug remained on the skin for twenty-four-hours to contaminate the blood sample.

RESULTS

In Fig. 1 are diagrammed, in terms of density of bacterial growth, the results of skin cultures taken on the infants in each group. The columns are divided into the percentage of infants in each group who

showed, on the day and in the area in question, either "none," "few," "moderate," or "abundant" bacterial growth on culture. When more than one type of organism was present on any one plate, that showing the heaviest growth was taken in assigning the culture to its place in the density scale.

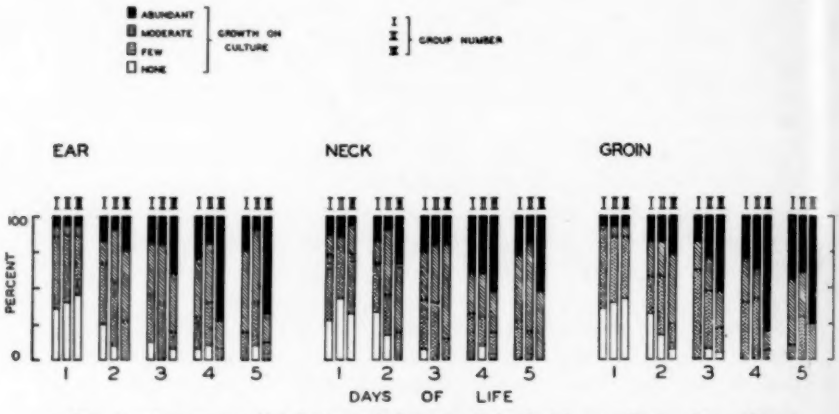

Fig. 1.—Percentage distribution of density of bacterial growth in skin cultures taken during the first five days of life from the areas indicated on three groups of newborn infants.

It will be seen that less than one-half of the infants in any group showed initial surface sterility in the areas cultured and that a few showed a heavy growth of organisms. The numbers of skin bacteria increased on the whole from day to day in each group. This was roughly parallel in Groups I and II. In Group III the increase was very marked, particularly behind the ear and in the groin.

The variety of organisms isolated and the per cent of cultures in which each was found is shown in Table I.

TABLE I

ORGANISM	GROUP I (%)	GROUP II (%)	GROUP III (%)
Staphylococcus albus	50.6*	57.4	76.8
Staphylococcus aureus	23.5	29.3	18.5
Beta hemolytic streptococcus	17.1	9.4	24.4
Alpha hemolytic streptococcus	7.1	7.5	3.7
Escherichia coli	2.4	4.4	2.7
Nonhemolytic streptococcus	0.0	5.0	6.7

*These figures do not take into account the density of growth, but each organism was found in numbers ranging from "few" to "abundant." *Bacillus subtilis*, which was found on the plates in a few scattered instances, is not included in the table.

Staphylococcus albus was the dominant organism, although not found in as high a percentage as in cultures from the adult skin.[6] In respect to both types of staphylococci, the cultures from Groups I and II showed about the same percentages, with Group III higher in respect to *Staph. albus*, and lower in respect to *Staphylococcus aureus*.

Beta hemolytic streptococci were present in about one-fourth of all cultures from Group III and less frequently in Groups I and II. The cultures from the faces of the infants in Group III, which are not included in the above table, showed beta hemolytic streptococci in 53.3 per cent of the plates. These organisms made their appearance as soon as the infant began to go out of the nursery for feeding.

Specimens of capillary blood, taken on eight infants in Group II at intervals of from five to twenty-four hours after the application of the sulfathiazole ointment, were all negative for the drug. One of the infants tested was one month premature, with a very thin skin, yet no absorption was demonstrable.

Two of the infants in Group I showed a scattered maculopapular rash twenty-four hours after the application of ointment. This eruption, which cleared up in three or four days, resembled the type that has been seen in this nursery on about one baby in twelve during the past two years under the routine use of ammoniated mercury. None of the infants in Group II showed any skin irritation during the first week of life. In Group III two infants had a rough, dry, very red skin for five and seven days, respectively, but none showed any eruptions.

DISCUSSION

The cultures taken in this study indicate that plain soap and water baths every other day are not effective in reducing or even holding in check the total numbers of bacteria on the newborn skin. This unexpected result may be due to mechanical factors, such as the lack of scrubbing, with consequent imperfect removal of debris from the skin.

Neither is ammoniated mercury, nor sulfathiazole, in the strengths used and applied once, able to arrest completely the growth of surface bacteria. Each, however, is more efficient in this respect than soap and water alone.

Suggestions of selective action from the percentages of Table I are as follows: The two drugs reduce the frequency with which *Staph. albus* is found to a greater degree than do soap and water; the latter are somewhat more effective than the drugs against *Staph. aureus;* sulfathiazole has the greatest effect on beta hemolytic streptococci; ammoniated mercury appears to be the most effective inhibitor to the growth of nonhemolytic streptococci.

The negative blood levels indicate that the intact newborn skin is impervious to such an application of sulfathiazole, so that no systemic reaction is to be expected from the drug when used in this fashion and concentration. If large areas of excoriation are present, some absorption will probably take place.[5]

The bacteria isolated from the infants reported here must represent essentially harmless parasitic strains, since they were present on the skin in large numbers without causing any signs of disease. There-

fore any attempt to evaluate the results of this study in terms of prevention of infective skin lesions rests upon the assumption that both virulent and harmless strains of the same organism would be affected alike by the treatment in question and would grow to the same extent in culture.

On such a basis, and considering also irritating effects on the skin, the three types of treatment studied here would rank in order of preference; sulfathiazole first, ammoniated mercury second, and soap and water alone last.

CONCLUSIONS

1. Repeated skin cultures on forty-three newborn infants during the first five days of life showed that one application of either 2½ per cent ammoniated mercury or 7½ per cent sulfathiazole ointment exerted a more marked retarding effect on the growth of skin bacteria than soap and water baths on alternate days.

2. Neither ointment produces an absolute decrease in the numbers of skin bacteria after twenty-four hours.

3. *Staph. albus* is the most prevalent organism on the skin during the first five days of life.

4. *Staph. aureus* and beta hemolytic streptococcus are also present on the skin in large numbers during the same time and in the absence of disease symptoms must represent harmless strains.

5. On the surface *Staph. albus* the two drugs exert a greater retarding effect than soap and water alone.

6. On the surface *Staph. aureus* the effect of soap and water appears superior to the two drugs.

7. On the surface beta hemolytic streptococcus sulfathiazole has a greater retarding effect than either ammoniated mercury or soap and water.

8. Sulfathiazole is not absorbed through the intact newborn skin in detectable amounts from a 7½ per cent ointment and does not produce skin irritation.

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TREATMENT OF CRYPTORCHIDISM

Report on Treatment in Thirty-Eight Cases With Chorionic and Pituitary Gonadotropin and Testosterone

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THERE are two main types of true cryptorchid cases. In the first type, structural changes such as a short spermatic cord, adhesions, or malformation of the path of descent hold the testicle or prevent its passage beyond a certain level. The testicle or scrotum may be malformed and incapable of responding to hormone stimulation. It is unreasonable to expect descent into a scrotal cavity that does not exist.[3] In the second type, there is a lack of endocrine stimulation and development so that descent is retarded.[1] In rare cases there is congenital absence of the testicle. The so-called "migrating type" is not included in this series. The testicles in these pseudocryptorchid cases are in the lower scrotum at times but slip up into the canals or abdomen.

The diagnosis[29] is usually not difficult. When it is impossible to palpate the testicle, it may be assumed, for purposes of treatment, that it is intra-abdominal. However, the testicle may be in some other location, entirely absent, or too small to palpate in the canal. The greatest difficulty arises with the "migrating type" as the testicles are often retracted before they can be seen or felt. They will often come down when the patient strains, coughs, or walks around. If in the canal they may be easily pushed into the scrotum.[59] When the testicles have never been in the scrotum, this part is not pendulous and saclike but is similar to a flat band.[10] The mother or father may have noticed the glands in the scrotum at times. If the child is not too young, he will know if the testicles have ever been in the scrotum and should be questioned on this point. The "migrating type" are in the lower scrotum at times and lie there naturally. Testicles that can be forced into the scrotum are classed as cryptorchid unless they have appeared naturally in the lower scrotum at some time. If the testicle is pulled down, it retracts as soon as released. A testicle in the upper scrotum is not fully descended. It is impossible to diagnose obstruction at an early age. When the testicle is firmly held and cannot pass a certain level, adhesions are

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The chorionic gonadotropin (Korotrin) was manufactured by Winthrop Chemical Company, Inc., New York, N. Y.; the pituitary gonadotropin (Gonadotrophic Factor) was manufactured by Ayerst, McKenna & Harrison, Rousses Point, N. Y.; and the testosterone propionate (Oreton) was manufactured by the Schering Corporation, Bloomfield, N. J.

probably present. Freely movable testicles are less likely to have mechanical obstruction. Adult cases can be assumed to have mechanical factors preventing descent.

As a boy goes through puberty the undescended testicle begins to atrophy. The spermatogenic tissues atrophy and fail to produce spermatozoa with resultant sterility.[65] In contrast, the testicle in the scrotum develops and begins to produce spermatozoa. The Leydig or hormone-secreting cells are not harmed as much as the sperm-producing cells, and some men with bilateral nondescent have a normal amount of male sex hormone while an occasional patient has the characteristics of an excess. Others are hypogonad in appearance and are definitely lacking in male sex hormone. Pace and Cabot[30] and Rea[49] give a histologic study showing the atrophy in the retained testicle in the adult from the second to the seventh decade.

Since it is harmful to allow these children to go through puberty without descent, treatment should begin not later than the prepuberty period if possible. This is an indefinite period, usually somewhere between the ages of 10 and 15 years. It is earlier here in California than in colder climates.

Einhorn and Rowntree[23] state that hypoplasia of the testicle is not formed under the age of 9 years, but that its incidence increases thereafter so that treatment should be carried out before the ninth birthday. McCrea[46] advises surgery at an early age rather than delay until puberty. Lowsley and Curtis[6] state that any time after the age of 4 years is suitable for surgical correction of this anomaly but that it should certainly be done before the onset of puberty. Deming[51] advises hormone therapy as early as 2 or 3 years of age if possible. Thompson and Heckel[12] state that since the testis normally resides in the scrotum and descends into it by the ninth fetal month, it is possible that better results would be achieved by treatment at an earlier age, perhaps shortly after birth. An important reason for hormonal therapy is found in its use as a therapeutic test, making it possible to differentiate between the obstructive and nonobstructive types.[2] Unnecessary surgery is prevented, and it is possible to do the necessary surgery before puberty has progressed and irreparable damage has resulted.[21] If operation is not performed before the scrotal testis has hypertrophied, the operated testis will remain smaller.[62] In adults the prognosis is poor with both hormonal and surgical treatment, but both methods should be used. The policy of postponement fosters an attitude of neglect. Parents are then likely to put off an operation until there has been irreparable damage to the testicle. When there is bilateral atrophy of the testicles in adults, substitution therapy with testosterone is advisable to counteract castration symptoms.[53, 70] It may be desirable to treat a child at a much younger age because of mental, physical, or endocrinologic conditions that this therapy would correct or prevent.[1, 17, 22, 58] Cryp-

torchid boys often become neurotic,[57, 66] and there may be associated behavior problems.[56] Men may become depressed, fearing a lack of sexual power and the inability to reproduce.[6] "The expectation of being normally sexed as adults is the inherent right of every child."[42] There is tremendous psychic shock to the boy who believes himself to be hopelessly abnormal during the first fifteen years of his life when he is developing mentally. A lack of vigor, strength, weight, muscular development, and masculine characteristics may accompany deficiency of male sex hormone and improve with treatment.[12] Lagging psychic development is speeded; lethargy is improved; effeminate traits are overcome; and weight is redistributed at times. Fröhlich's syndrome and other endocrine conditions are common. If the genital organs are small, treatment may be given to increase their size.[26] Davidoff[47] treated twenty-one abnormal children for cryptorchidism with occasional improvement in the mental status, but psychiatric therapy was also employed.

Care should be exercised not to increase the size of the genitals above normal for the child's age or cause pubic hair growth in the pre-adolescent.[55] However, Dorff[17] states that precocious development, above average for age, is not harmful and regresses with cessation of therapy. The enlargement of the genitals can be stopped at any level by discontinuing treatment.[12] Sex should not be unduly stimulated. This is rarely a problem. Testosterone is more likely to cause trouble. Cutting down the dosage is usually sufficient. If trouble persists, treatment should be discontinued for a time. Other children with erections and sex irritability are improved after treatment. Cases have been observed that are better following puberty.

The percentage of good results varies with the different reports in the literature from 16 to 100 per cent.[2, 23, 27, 28] The high percentages are with a very small series of cases. Bigler, Hardy, and Scott[36, 37] reported the results of eighteen investigators who found descent in 62 per cent of 267 testicles in 191 patients. In their own series of seventy-one cases there was complete descent in 45 per cent of the testicles. Nixon[38] reviewed the literature and found 59 per cent descent of testes in 388 boys. Of fifty-nine boys treated by himself, there was descent in 33 per cent. Thompson and Heckel[39] analyzed twenty-seven reports covering 579 patients in which 61 per cent of the testicles descended. They treated fifty patients with only 20 per cent descent. The prognosis is not as hopeless as some would imply.[15]

Other parts of the genitals may enlarge under endocrine therapy.[26] The vas deferens lengthens; the vascular supply to the testicle increases; the scrotum,[28] epididymis, prostate,[60] and seminal vesicles increase in size. These changes should be an advantage if surgery is required. Small parts make an operation difficult. It is frequently impossible to obtain a satisfactory result when the spermatic cord is short.

TABLE I

CRYPTORCHID CASES

CASE	YEAR TREATMENT BEGAN	AGE	BODY TYPE	RIGHT TESTICLE BEFORE TREATMENT	LEFT TESTICLE BEFORE TREATMENT	RIGHT TESTICLE AFTER TREATMENT	LEFT TESTICLE AFTER TREATMENT	DOSAGE TWICE WEEKLY: CHORIONIC GONADOTROPIN (I. U.)	DOSAGE TWICE WEEKLY: TESTOSTERONE (MG.)	DOSAGE TWICE WEEKLY: PITUITARY GONADOTROPIN (R. U.)*	CHORIONIC GONADOTROPIN (I. U.)	TESTOSTERONE (MG.)	PITUITARY GONADOTROPIN (R. U.)*	REMARKS
1	1938	7	Fröhlich	C	C	S	S	100			500			Testicles came down as he got older; hypospadias
2	1941	21	Normal	A	A	C	C	250	15		17,500	855		Operated on
3	1939	13	Short	C	S	S	S	500			6,000			Bone age, 9½ years; right hydrocele
4	1938	3	Normal	A	A	A	A	200		50	6,600		2,900	Nervous
5	1940	10½	Fröhlich	A	A	S	S	500			8,000			Mons covered penis
6	1941	13	Fröhlich	A	A	S	S	500	5		22,000	160		Mons covered penis
7	1939	4	Normal	A	A	A	S	500		100	17,500		12,000	Left hydrocele; left breast enlarged; large penis
8	1938	4½	Normal	S	C	S	C	500	10	100	5,700	160	3,400	Retarded at school; improved; surgery advised
9	1940	11	Fröhlich	C	S	S	S	500			5,500			Too short
10	1942	9	Fröhlich	C	C	S	S	500	5		6,000	30		Penis developed rapidly
11	1939	4	Normal	S	A	S	C	500			15,000			Enlarged thymus; enuresis
12	1941	12	Fröhlich	A	A	S	S	500			5,500			Very small penis
13	1937	8	Fröhlich	A	S	S	S	100			2,400			Right hydrocele
14	1942	5	Normal	C	S	S	S	250			6,250			Enuresis
15	1937	9½	Slender	C	C	C	C	500	5	100	8,800	110	1,150	Timid; acts like younger child; surgery advised
16	1934	31	Eunuch	A	A	A	A							Sterile; no beard

17	1939	9½	Normal	C	S	C	S	200			900			Operated on; good result
18	1940	11	Short	C	C	S	S	100	5		1,000	50		"Migrating type"
19	1938	10½	Fröhlich	A	S	S	S	250			2,800			Called a "sissy"
20	1940	10½	Fröhlich	S	A	S	A	500			9,000			Called a "sissy"; surgery advised
21	1937	13½	Fröhlich	S	C	S	S	100			2,500			Right hydrocele
22	1942	2	Normal	S	A	S	C	250			2,500			Large penis developed
23	1942	9½	Normal	S	A	S	C	500	5		9,000	35		Nervous; surgery advised
24	1938	11	Slender	C	S	S	S	500			12,000			Retarded school work
25	1942	10	Fröhlich	A	S	S	S	250	5		6,750	135		Left varicocele
26	1939	13	Fröhlich	C	S	S	S	1,000	7½	150	27,500	7½	3,450	Tiny mons covered penis
27	1942	12½	Fröhlich	C	C	S	S	500	5		4,500	144		Retarded at school
28	1941	12	Fröhlich	A	S	S	S	500	10		9,500	190		Left hydrocele; testicle in upper scrotum before treatment
29	1939	5	Fröhlich	C	S	S	S	500	5		11,800	70		Penis covered by mons
30	1941	10	Fröhlich	S	A	S	C	500	5		11,500	185		Surgery advised
31	1940	8	Normal	A	A	S	S	500			17,000			Improved after long intermittent treatment
32	1939	11	Short	C	S	S	S	500			5,500			Bone age, 8½ years
33	1942	8	Normal	A	C	S	S	500			4,000			Normal boy
34	1938	7½	Fröhlich	A	A	S	S	500			12,000			Penis nearly covered by mons
35	1942	8½	Slender	A	A	S	S	500	2½		8,000	40		Problem child
36	1937	4	Normal	C	C	S	S	100			1,200			Enuresis; habit spasms
37	1942	9	Slender	C	C	S	S	500	5		500	50		Pseudocryptorchid?
38	1939	13	Normal	C	C	S	S	1,000		300	28,500		3,600	Pubic hair; well developed
39	1934	13	Fröhlich	C	C	S	S	Operation						Enuresis; no hormone treatment
40	1941	8½	Fröhlich	O	S	O	S	250	5		8,000	60		Treatment after hernia operation caused atrophy right testicle
41	1939	12	Fröhlich	S	A	S	C	500	10		14,000	240		Left hydrocele; surgery advised
42	1942	3½	Normal	C	C	S	S	250			3,250			Asthma
43	1942	35	Slender	?	?	S	S	500	10		7,500	150		Treated after operation, age 31; sterile
44	1938	3	Normal	A	S	S	S	500			21,000			Right testicle in upper scrotum after treatment
45	1942	8½	Normal	C	C	S	C	500	5		4,250	40		Large penis
46	1940	9	Normal	A	S									Surgery advised; large penis; excess hair; hernia
47	1941	21	Obese	?	?	S	S	250	5		2,500	150		Treated after bilateral surgery

A, Intra-abdominal.
C, In canals.
S, In scrotum.
O, No testicle present.
*Collip.

Reports of operative results[40] in the literature show a variation in the percentage of cures ranging from 42 to 92 per cent.[23, 25] A good prognosis with normal size and position of the testicle probably does not average more than 50 per cent, although in skillful hands the percentage is higher.[68] The results are good, however, considering parental neglect until too old and the patients operated on with parts that are small, malformed, or absent.

The patients who are reported in this series were referred by other doctors and therefore were predominantly endocrine in type. Only those treated since 1937 were a part of this study; the cases from 1930 to 1937 were not included. Diets, thyroid, and other endocrine treatments were administered in addition to that listed in Table I.

DISCUSSION AND RESULTS

The list of cases in Table I included only those patients under observation or treatment either preoperatively or postoperatively in the endocrine department. The results in the patients treated exclusively in the urologic or surgical departments were not included in this paper. Many of the operations were performed by private physicians before the patient came to the clinic. There were two patients with hernia, six with hydrocele, one with varicocele, and one with hypospadias. These anomalies of development are rather common in cryptorchid cases. The genitals were smaller than average for the age in most instances before treatment. Thyroid, pituitary, or other endocrine deficiencies were frequently present. There were twenty cases of Fröhlich's syndrome. Five patients were underweight. Three patients were too short—of a hypopituitary type. The enuresis noted in four patients was improved. Some of these boys were weak, easily tired, not inclined to play games well, likely to associate with younger children, and often classed as "sissies" by their fellow schoolmates. There was a tendency for the boys to act like younger children, to keep to themselves, and to have few close friends. Their attention and concentration was poor. They were nervous, irritable, and uncooperative, frequently having trouble with their school work. A feeling of inferiority was prevalent, with occasional boastfulness and temper tantrums. Occasionally they were classed as definite problem children.

Other children were inclined to be very cruel. Boys said that they had been looked upon as abnormal and made the subject of embarrassing remarks by schoolmates. To prevent this trouble they hid their secret for years and went to great lengths to avert discovery. One boy said he got along all right in school until he was lined up with other boys in the nude in the gymnasium. The school doctor inspecting the children thoughtlessly remarked, in the others' presence, that he had no testicles and a very tiny penis. Other of the boys presented no special problems. They were of average mental and physical development for their ages. They played well and got along well in school.

The cost of chorionic gonadotropin is low in comparison with other preparations that are used for cryptorchidism. Adequate hormone therapy need not be expensive, and hospitalization is not required. The injectable liquid is prepared fresh, daily, from the dry material purchased. It is standardized in international units. The rat unit, previously used, varied in strength, depending on the method of standardization of the manufacturer.

There was both a mental and a physical reason for treating some of these patients prior to the prepuberty period. The time to start treatment had to be individualized. Why wait for nature to improve some of these deficiencies at puberty that can be corrected when they are discovered? The first fifteen years are the most important in the mental and physical development of the child.

The male sex hormone lengthens the urethra, enlarges the prostate, and increases the bladder and sphincter musculature. Thus the child has greater urinary capacity and better control. Essentially the same transition occurs at puberty, during which time enuresis undergoes a spontaneous cure. The problem cases should be searched for and treated until the boys feel they can take their place with the rest of the classmates. When worried they should be reassured regarding a normal sexual and marital life and, if possible, regarding sterility. A prognosis of sterility should not be given until the boy has gone through puberty and every means, including surgery, has been used to prevent it.

Results of treatment are summarized in Table II; prognosis, in Table III.

The following reasons are given for leaving out nine patients not included in figuring the percentage of results. A patient (Case 17) with one testicle in the canal was operated on at the age of 11½ years after only 900 I. U. of chorionic gonadotropin, with a normal scrotal testicle resulting. A patient (Case 39) with both testicles in the canals was operated on at the age of 13 years after observation without treatment. The result was good. A patient (Case 40) with a right inguinal hernia was operated on at the age of 8½ years without treatment, but it was impossible to save the testicle. He was treated postoperatively for Fröhlich's syndrome. The patient in Case 46 had priapism, large penis, and excess body hair. Because of this and right inguinal hernia, surgery was advised for the right testicle rather than hormone therapy. It was believed that there was excessive androgen production and that delay would be harmful. The birth weight was two and one-half pounds. There was urinary incontinence during the day. The patient in Case 47 was added to show that adults, previously operated on but still having underdeveloped genitals could be treated and additional improvement attained. This patient, 21 years of age, was obese with a penis one-half of the average size and hard spherical testicles two-thirds of the average size. The testicles and penis definitely increased in size, and hair began to grow on his chin

TABLE II

	NUMBER	PER CENT
Bilateral cases		
Complete descent of both testes		
Intra-abdominal	7	18
In canals	8	21
Complete descent of one	2	5
No descent	2	5
Unilateral Cases		
Complete descent		
Intra-abdominal	4	10.5
In canals	8	21
Partial descent	5	13
No descent	2	5
Cases		
Total	38	
Total with complete descent	27	71
Total with complete descent including descent of one	29	76
Partial descent	5	13
No descent	4	10.5
One normal testicle in scrotum	36	95
Testicles		
Total undescended	57	
Total number with descent	44	77
Total with partial descent	5	8
Total with no descent	8	14
Fröhlich's syndrome cases	18	
With complete descent	15	83

TABLE III

PROGNOSIS IN THIS SERIES OF PATIENTS

CONDITION	CHANCES OF IMPROVEMENT
Hormone production of testes in scrotum	Good
Hormone production of testes undescended	Fair
One underdeveloped testicle in scrotum	Good
Development of bilateral scrotal testicles	Good
Development of penis	Good
Stopping migration	Good
Descent with puberty	Good
Descent with obstruction	None
Neurosis due to genital condition	Good
General physical improvement	Good
Gain in weight and height	Good
Fertility of descended testicle	Good
Fertility of undescended testicle	Poor

and in the sideburn areas during treatment. Three patients were classed as being too old. The patient in Case 43 was operated on without treatment at the age of 31 years after both testicles had atrophied. When observed four years later, practically no testicular tissue could be palpated. He was sterile and had very little hormone production. The patient in Case 16 was examined at the age of 31 years in 1934. No testicles were palpable. He was sterile and of the eunuch type. He could not return for treatment. This patient was included to show the pathetic nature of some of these neglected conditions. The patient in Case 2, 21 years of age, was given considerable treatment. The tes-

ticles came down into the canals and enlarged. He could still push them back into the abdomen which he did at times because of pain. There was definite obstruction at the lower part of each canal. The penis was small before treatment and developed to normal size. He was hairy and masculine in type. However, puberty did not bring the testicles into the canals or increase their size as did endocrine therapy. He was referred to a urologist for operation. The left testicle was brought down into the scrotum, but the ductus deferens could not be preserved. The testicle was about the size of a medium-sized olive and remained a little high in the scrotum. He had to go east but intended to return in a year to have the other side operated on. Hormone production appeared good. The patient in Case 18 was listed as an example of the "migrating type." The testicles were in the bottom of the scrotum at times.

That chorionic gonadotropin caused descent in part of the cryptorchid cases was beyond doubt. There was a question as to whether the addition of pituitary gonadotropin increased the incidence of descent. Testosterone, when added, further enlarged the parts, and this was an indication for its use. It speeded up the results and it might cause a slightly higher percentage of cure. It had a definite effect on the patient's general mental and physical condition which was more striking than that obtained from chorionic gonadotropin alone.

There was complete descent in 76 per cent of the patients and partial descent in another 13 per cent, making a total of 89 per cent with some movement of the testicle toward the scrotum. The other 11 per cent without descent showed some enlargement of the genitals as judged by the size of the testicle, scrotum, and penis. The high percentage of results was believed to be due to fresh solution made from dry powder, the larger five hundred international unit dosage, the high incidence of nonobstructive types, and the prevalence of endocrine and hypogenital cases. The testicles usually increased in size, even those that did not descend. In no incidence did a testicle become smaller or appear to degenerate. The penis usually increased in size a little. In some patients, particularly where testosterone was used, there was a marked increase in size of the penis. In patients with Fröhlich's syndrome, where the tiny penis was entirely covered by the mons, there was marked improvement. It was always possible to enlarge the penis to normal size. Quite a variation in size was considered normal, and the penis was classed as small, medium, or large normal. Only in three instances was the penis enlarged a little above normal size for the age. In the first patient chorionic gonadotropin and pituitary gonadotropin had been given. Other factors were thought to have played a part as one breast was enlarged a little, and the testicles were still small. In the second patient chorionic gonadotropin was believed to have been the cause through testicular stimulation. Growth in the patient in the third case was caused by testosterone in 5 mg. doses. Further growth did not

occur after treatment was discontinued. Only in the first patient did the parents feel that the size of the penis was too large. After further growth in general, the size was normal for the child's age. If these children are examined routinely, excessive enlargement can be prevented by stopping treatment. Pubic hair growth did not occur until about the age of puberty. Younger children were not given enough treatment to cause hair growth.

In the patients under observation through puberty, the testicles became normal adult size in every case that had descended. This result cannot be expected following surgical descent due to infections, adhesions, injury to blood and nerve supply, and other unpreventable surgical hazards, so that surgical treatment should only be used after hormone failure. An orchidopexy, then, should be insisted upon.

Following treatment the boys became more muscular, played better, became broader through the shoulders, and were generally classed by their parents as "more boy" in type. There was a gain in weight and height[17] when the children were normal or underweight, with a striking improvement in their appearance.

After treatment the problem children took orders, cooperated, and developed a more mature attitude. There was increased dependability and fulfillment of necessary tasks with better grades at school. These improvements, mental and physical, were more marked in the patients where testosterone was given. The patient in Case 35 was an example of an extreme type. This problem child had been expelled from school for the last four months of the year because of uncontrollable behavior, extreme distractability, short span of attention, and aggressive behavior toward other children. He kicked his father severely when his clothes were removed for examination, kicked the nurses, spitting at them, and knocked bottles and instruments on the floor breaking some. He became very much better with treatment, actually cooperative. The tantrums stopped. It was no longer necessary to hold him for injections. He came to the office willingly because he wanted to continue treatment. The patient in Case 8 was extremely nervous. He had trouble with the other children because of his condition and became so irritable that he finally antagonized his teachers. When testosterone was given, his character completely changed. He became "like other boys." The prejudice at school remained, however, and he was finally transferred to another school. He then got along well with both pupils and teachers and received good grades.

SUMMARY

Cryptorchidism without mechanical obstruction may be corrected with hormonal therapy. The testicles descended in 76 per cent of the patients treated in this series. Since the number of patients with obstruction varies, and it is usually impossible to diagnose which patients have obstruction, the prognosis varies. With endocrine

treatment, obstruction can be diagnosed early so that the necessary surgery can be performed not later than the prepuberty period, thus preventing the atrophy that occurs in the testicle which is allowed to go through puberty undescended. Certain mental and physical conditions make it advisable to treat some of these boys at a younger age. When descent does not follow treatment, orchidopexy must be used to prevent sterility, hypogonadism, complications, and possibly malignancy through earlier diagnosis. Operation should be facilitated by treatment that lengthens the spermatic cord and enlarges the scrotum and testicle. There was no harm to the testicles that could be detected, regardless of the age at which the boy was treated.

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PEPTIC ULCERS IN INFANCY AND CHILDHOOD

Post-Mortem Studies of Eight Cases; One Case of Possible Poisoning by Rhubarb

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FOR many years it was the opinion of most physicians that gastric and duodenal ulcers occurred so rarely in young children that they could be disregarded in diagnosis. That opinion has been changed considerably since Holt's[1] paper in 1913, in which he reviewed ninety-five cases of ulcer in childhood, and since Proctor's[2] statement in 1925, that about 2 per cent of all cases of ulcer had symptoms dating back to childhood. At the present time the literature contains increasing numbers of cases of ulcer in childhood so that the condition is coming to be regarded as of possible importance even in early infancy.

Kennedy[3] states that ulcers in children fall into fairly distinct groups, as follows: (a) Ulcer of the newborn infant which is identified by melena and either heals rapidly or goes on to rupture or hemorrhage; (b) ulcers in young infants which appear to have epidemic incidence and may be associated with exanthematous diseases; (c) ulcers in children between 1 and 9 years of age which are of adult type but do not produce typical symptoms; and (d) ulcers in older children which are entirely similar to those seen in adults as to both symptomatology and pathology. Holt[1] found that the greatest incidence of ulcer in childhood was between 6 weeks and 5 months of age, with 70 per cent occurring in that age period; only 10 per cent were reported in the neonatal period.

The question of the etiology of ulcers in infants and children is, apparently, as unsettled as is the question of the etiology of ulcers in adults. Thiele,[4] Conklin,[5] and others[1, 6] emphasize that in the newborn period it is probable that ulceration results from trauma, from vascular accidents, or from spasms at the time of birth. Shore,[7] who states that even in somewhat older infants vascular injury may lead to ulceration, has suggested that overdistension of the stomach by large feedings may cause rupture of small vessels which may be followed by ulceration of the mucosa. Veeder[8] and Guthrie[9] note that in infants ulcers are found most frequently on the posterior walls of the stomach and duodenum. These authors believe that food stasis may be a significant factor. Krafft[10] suggests that there may be an association between the development of ulcers and the onset of hydrochloric acid secretion in the stomach. In this connection, Miller[11] has found that the acid, which is high in the first twenty-four hours of life, falls steadily to

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about the tenth day, after which time it remains quite stationary. A number of authors[4, 6, 9] noting an association between ulcers and marasmus consider that poorly nourished infants are most apt to develop these lesions. Veeder,[8] on the other hand, has suggested that it is more probable that ulcer is the cause rather than the effect of chronic nutritional disease. Proctor[2] mentions that in older children the ingestion of foreign bodies or caustics, trauma, and the various exanthematous diseases may be exciting causes of ulcer, but that the lesser incidence of the condition during childhood may be due to the fact that worry, strain, alcohol, highly seasoned foods, and tobacco usually are not factors to be considered.

In childhood the symptoms of ulcer vary from complete absence to the typical syndrome as seen in adults. Holt[1] has reported that in his cases one third of the patients gave no significant gastric history. Vague gastric distress, failure to gain in weight, the presence of blood in stools or vomitus, and belching have been mentioned in a number of reports;[8, 9, 12] when any or all of these symptoms are present, a diagnosis of ulcer should be considered and an attempt made to substantiate the diagnosis by means of radiographic studies. Shore[7] emphasizes that in children ulcers are usually acute, so that symptoms, whether typical or bizarre, are likely to be acute and severe. Proctor[2] concurs in this opinion but adds that close questioning will frequently reveal a long but rather vague history of epigastric distress, periodic vomiting, and constipation. Furthermore, whenever there is sudden collapse in an infant or child, the possibility of perforation of an ulcer must be considered.

Bird, Limper, and Mayer,[13] who have analyzed reports of several hundred cases of ulcer in childhood as reported in the literature, state that it may be prognosticated that in the newborn infant most ulcers will bleed seriously or perforate. They found that there might be little in the history or condition of the infant to suggest the presence of an ulcer before the hemorrhage or collapse occurs. After 2 years of age the nature of the disease has been observed to change, with resulting symptoms of some kind usually antedating hemorrhage or perforation. In addition, a number of cases will give evidence of pylorospasm or stenosis. Beyond the age of 7 years hemorrhage in less common and symptoms of pyloric stenosis and perforation are more often seen. In those cases in which a diagnosis can be made before serious complications occur, it may be possible to treat the child medically and thus bring about healing of the ulcer,[6] but most authors agree that surgery may be the only hope in young infants. However, since bleeding occurs in about 40 per cent of all childhood ulcers,[2] surgery should not be delayed too long in any case. In reports of about 119 operations on children having ulcers and showing hemorrhage, perforation or pyloric stenosis have been reported, including a number in which good results have been obtained.[13]

Pathologically, the ulcers seen in childhood are similar to those seen in adults. If they are chronic in type, the appearance in no way differs from that of chronic ulcers in adults. However, in young children ulcers are more commonly of the acute type, while in very young infants they may be associated with necrosis and hemorrhage into the surrounding tissues rather than with inflammation. The location of ulcers in children is a point of interest as the majority are found to be in the duodenum; the literature contains only twenty-five cases[14] in which ulcers were found which satisfied the criteria of Foshee[15] as being both chronic and gastric, whereas the total number of all kinds of ulcers is about 300.[13] No figures are available as to the number of acute gastric ulcers reported.

During the past six years, eight cases of peptic and duodenal ulcer have been seen in the course of about 500 routine autopsies on infants and children at the Colorado General Hospital (1.6 per cent). It is my intention to add these cases to those already reported in the accumulating literature, thus helping further to clarify the picture of ulcers in childhood.

CASE 1.—This infant was a white male who died suddenly on the second day of life. No history was known except that the mother suffered from severe nausea and vomiting throughout her pregnancy; the birth was entirely normal. The autopsy done on the baby revealed an early pneumonia and otitis media which were probably contracted during birth, some toxic degeneration of the kidney tubules, and, in the duodenum, a well-developed ulcer which extended through the mucosa and into the muscle layers almost to the serosa. The ulcer showed extensive inflammation with necrosis, leucocytic infiltration, and edema. There was no evidence of repair by fibrous tissue.

CASE 2.—This 3-day-old white female infant was delivered at home and appeared to be entirely normal at birth. She was brought to the hospital on the second day of life because of failure to retain any food or water and because the urine was scanty and dark. She died a few hours after admission to the hospital. The autopsy revealed hypodevelopment of the left heart, a bicornate uterus, fatty infiltration of the kidney tubules, esophagitis, hemorrhagic erosions throughout the stomach and intestines, and also, an extensive ulceration of the first part of the duodenum. The ulcer extended into and almost through the muscle coats; there was hemorrhage into the remaining and adjacent muscle as well as on the mucosal surface where it was associated with a fibrinous membrane. Inflammation was not a marked feature, but there were small numbers of lymphocytes at the borders of the ulcer; the surrounding tissues were edematous.

These two cases were our only ones seen in the neonatal period. It is unfortunate that in Case 1 we have no detailed history of the infant's short life so that we know nothing of any symptoms or findings which might have suggested a diagnosis of ulcer. The extent of the ulceration as seen at autopsy indicates that melena or some evidence of pain might have been observed during life.

Case 2 is of special interest because of the rather definite clinical history of gastric symptoms even in such a young infant. The pathologic findings indicate that the primary factor was either a traumatic or a

spontaneous hemorrhage into the duodenal wall with subsequent ischemia and ulceration of the mucosa. It is probable that blood was present in both the vomitus and stools during life although it was not identified.

As was stated previously, neonatal ulcers of the stomach and duodenum are believed to be due to vascular accidents accompanied by ischemia of the mucosa and are characterized by necrosis of the tissues without inflammation. The two cases reported here are of interest in that the one (Case 2) fits nicely into the above theory, being unusual only in the definiteness of the symptoms produced, whereas the other case (Case 1) showed more than a destructive necrosis and was definitely inflammatory in nature.

CASE 3.—This 2-month-old white male infant was admitted to the hospital because of severe pertussis complicated by bronchopneumonia. There was no history of gastric symptoms before admission and no evidence of any during the child's stay in the hospital, with the exception of some terminal anorexia and abdominal distension. At necropsy, pneumonia was found as well as degeneration of some of the nerve cells of the cerebral cortex. This latter finding suggested the cerebral changes which may be seen in some cases of pertussis and convulsions. There was no true ulcer present, but in the duodenum there was a small puckered area in which Brunner's glands were absent and, in addition, there was one markedly dilated cystic mucosal gland filled with polymorphonuclear leucocytes.

Inclusion of this case in the series may be open to some question, but the absence of Brunner's glands suggests that there was, at some previous time, a small ulcer in this area and that its healing left a small cystic mucosal remnant which became inflamed in the course of the final illness; had the child lived for a longer time it seems probable that a definite ulcer might have developed at the site of the previous one.

CASE 4.—This patient was a white boy, 14 months of age, who was admitted to the hospital because of fever, listlessness, and vomiting of three weeks' duration. There was a past history of measles and of vaccination against smallpox. In the hospital the child became progressively worse, developing symptoms and findings typical of tuberculous meningitis. He took his food well until about three days before death, when he refused all nourishment. The autopsy showed the expected tuberculosis. In the duodenum there was a superficial ulcer which was moderately infiltrated with leucocytes; it involved the mucosa only, and hemorrhage was not a prominent feature.

This case represents a fairly large group in which ulcer may be considered to be a late or terminal occurrence, secondary to more serious illness. There was no evidence of any tuberculous changes in the ulcerated area itself, but it is possible that tuberculous involvement of adjacent vessels may have been responsible for the development of the ulcer. Furthermore, the frequent association of ulcers of the gastrointestinal tract with meningitis makes it necessary to consider disease of the central nervous system as of possible significance in the production of this ulcer.

CASE 5.—A boy, 3 years of age, entered the hospital suffering with abdominal cramps, vomiting, and diarrhea which followed the eating of raw rhubarb leaves. On admission his temperature was normal and his urine showed a 2 plus albumin as well as occasional casts and red blood cells. There was no evidence of abdominal tenderness. On the third hospital day his white blood count was found to be 17,300; the blood sugar, 292 mg. per cent; blood nonprotein nitrogen, 164 mg. per cent; blood urea nitrogen, 132 mg. per cent; and blood creatinine, 6 mg. per cent. His temperature rose to 100° F. on the third and fourth hospital days but was nearly normal at all other times. He continued to vomit, and after the third day the vomitus contained old blood, and the stools were tarry. On the fourth day he had a number of convulsions. Urinalysis at this time was normal. On the sixth day the blood chemistry was repeated and found to be as follows: blood sugar, 106 mg. per cent; blood nonprotein nitrogen, 176 mg. per cent; blood urea, 152 mg. per cent; blood creatinine, 7.8 mg. per cent; blood phosphorus, 6.5 mg. per cent; blood calcium, 8 mg. per cent; and serum carbon dioxide combining power, 31 volumes per cent. After the seventh day the vomitus contained fresh blood with clots in considerable amounts. He died on the tenth hospital day after becoming progressively worse and failing to respond to any treatment.

At autopsy the only striking finding was a very large ulcer in the first portion of the duodenum. This ulcer showed severe necrosis, extended into the pancreas, and contained a large eroded vessel, the wall of which was necrotic. Inflammation was marked, the ulcer appearing to be of the chronic type usually seen in adults in a stage of acute exacerbation.

There is little doubt that massive hemorrhage from the large duodenal ulcer was a factor in bringing about the death of this boy. However, it is not possible to evaluate thoroughly the importance of the other factors involved which were (a) the significance of the raw rhubarb leaves as a poison, and (b) the very high degree of nitrogen retention in the blood. In cases of fatal poisoning due to the eating of rhubarb leaves reported in the literature,[16, 17] the noxious agent has been found to be oxalic acid. Ulcers have not been mentioned, nor have blood studies been reported. Because of the similarity between the findings in this case and in cases of poisoning by mercuric chloride, we questioned the possibility of some corrosive having been used as a spray on the rhubarb, but there was no history of any such substance having been used. In order to check further the possibilities of poisoning in this case, rhubarb leaves from the same patch were fed to two guinea pigs, which was followed by the death of both animals in a few days with hemorrhagic erosions of the colon but without evidence of any pathologic changes in the upper portion of the alimentary tract. The experiment was repeated with more material from the same patch as well as leaves from other patches, but we were not able to duplicate the findings, so that it is not certain whether or not the two animals can be considered to have died from the effect of the rhubarb or from some other condition.

Since it is well known that pathologic lesions in the tissues of children may advance very rapidly, there is some possibility that a corrosive action associated with the rhubarb may have initiated the ulcer. But, on the other hand, the appearance of the ulcer, both grossly and mi-

croscopically, suggested that it was of the chronic type with erosion into the pancreas, some evidence of fibrous healing, and extensive inflammation. Thus, it seems most probable that an ulcer of long standing was activated by the gastric upset following the ingestion of rhubarb leaves. The absence of any history of previous gastric symptoms may have been due to lack of adequate observation.

CASE 6.—A boy, 9 years of age, was admitted to the hospital because of an injury to his foot. A splinter of wood had penetrated the deep tissues and, in spite of seemingly adequate treatment, the child developed tetanus. There was a history of measles, scarlet fever, and pertussis when the boy was about 1 year of age. No history of gastric symptoms was obtained. Death was the result of tetanus, the post-mortem findings being consistent with that condition. In the first part of the duodenum there was an area in which there was a deep indentation of the mucosal wall, absence of Brunner's glands, thinning of the submucosal tissues, and slight lymphocytic infiltration; the superficial epithelial covering was intact. This area was believed to be the scar of a healed duodenal ulcer.

It is impossible at this time to determine just when the ulcer was active, but it seems probable that it originated in connection with one of the exanthematous diseases from which the boy suffered at 1 year of age, since he had no other history of significant illness. Thus, this case suggests the possibility that duodenal and gastric ulcers may appear as complications of the various childhood diseases. It also emphasizes the fact that children may develop ulcers which heal spontaneously without specific treatment.

CASE 7.—A 10-year-old white female entered the hospital with a history of severe abdominal pain and vomiting two weeks before admission. Laxatives had been given, and the child had become increasingly ill. Her past history included measles, chicken pox, pertussis, sore throats, and an attack of rheumatic fever at 6 years of age. On entrance, a diagnosis of bronchopneumonia was made as well as a diagnosis of probable ruptured appendix. Her heart was at the upper limit of normal in size, and a blowing systolic murmur was present. No edema was noted, though there was a report of occasional swelling of her ankles.

In the hospital the child's condition improved; the pneumonia cleared, and her electrocardiogram was considered to be normal. Two weeks after admission a superficially inflamed, retrocecal appendix was removed with difficulty after freeing many adhesions. Following the operation the child did poorly, the wound opened, and cultures positive for *Clostridium welchii* were obtained from the discharge. Her heart was enlarged slightly, and a faint presystolic thrill as well as ventricular extrasystoles were noted. She died fifteen days after operation.

The findings at autopsy included peritonitis, mesenteric and pelvic abscesses, paralytic ileus, and rheumatic carditis, both acute and chronic. In addition to the above findings there were multiple small ulcers located along the lesser curvature of the stomach, the largest of these measuring about 3 mm. in diameter. Microscopically the ulcers were seen to involve both mucosa and submucosa and, in some instances, to extend into the muscle. They showed both necrosis and inflammation.

This is the only case in the present series which showed definite ulceration of the gastric mucosa. It is, however, a case in which the ulceration was acute, probably terminal, and secondary to the severe infectious disease of the patient.

CASE 8.—This 11-year-old white male was admitted to the hospital suffering with otitis media and meningitis. He gave no history suggestive of disease of the gastrointestinal tract. At the onset of his illness he vomited frequently but, as he was receiving sulfanilamide and also was suffering from mueningitis, the vomiting was considered to be related to either the drug or infection. On the seventh day of illness the boy suddenly went into profound shock. Following this he vomited large amounts of blood and had numerous tarry stools. He died on the tenth day after admission to the hospital. Autopsy showed the expected meningo-encephalitis as well as a duodenal ulcer, which was 1 cm. in diameter, had fairly firm edges, and extended into the pancreas. This ulcer did not show any gross bleeding point, but microscopic examination revealed very severe inflammation and necrosis which involved numerous small vessels. A number of thrombosed vessels showed almost complete necrosis of their walls.

In this case it is highly probable that the ulcer was of the chronic type which may well have produced some unrecognized gastrointestinal symptoms previous to the onset of the terminal illness. The marked degree of necrosis and inflammation present in the ulcer after death indicates that there had been a recent extension of the lesion, however. Death was due, in all probability, to a combination of the infectious disease of the central nervous system and to massive hemorrhage from the duodenal ulcer.

DISCUSSION

In the eight cases reported in this paper there were only two in the newborn period (Cases 1 and 2). One of these cases was unusual in that there was a fairly definite history of complaints suggestive of disease of the gastrointestinal system, although the infant was only 3 days of age. This case was the only one in the group in which there was any history suggestive of ulcer, but the lack of such history in the older children may have been due, at least in part, to inadequate questioning of the parents in regard to vague complaints. The other case (Case 1) was remarkable in that severe inflammation was present in the ulcer, which is a rare finding in this age period when ulcers are thought to be due almost exclusively to vascular accidents at the time of birth.

In two cases (Cases 4 and 8) ulcers were found in association with severe infectious disease of the central nervous system. It is believed by many that there is some definite connection between disease of the brain and its coverings and lesions in the gastrointestinal tract, the brain condition being of some etiologic significance. In one of these cases (Case 8) the appearance of the ulcer indicated that it was of the chronic type, suggesting that it antedated the onset of the disease of the nervous system.

Cases 3 and 6, showing only scars of previous ulcers, are included to emphasize the possibility of ulcers occurring without symptoms and healing without specific treatment. Absence of Brunner's glands and mucosal indentation were considered as evidence that an ulcer was present at some previous time and had healed.

One case only (Case 7) showed lesions of the gastric mucosa. In this instance the multiple ulcers were probably terminal, resulting from the severe infection from which the child suffered.

Case 5 is of remarkable interest and deserves special consideration because of the association of ulcer with possible poisoning by rhubarb leaves. The reports of rhubarb poisoning as found in the literature deal with the eating of cooked greens in which the noxious agent has been found to be oxalic acid. No ulcers subsequent to rhubarb poisoning were present in any of the patients in the reported cases, and no work has been found which would indicate whether or not there may be some other toxic or corrosive substance present in the raw leaves.

Seven patients of the eight cases reported showed ulcers located in the duodenum.

SUMMARY

Seven cases of duodenal and one of gastric ulcers in children from 2 days to 11 years of age have been reported. One case was remarkable because of the association of ulcer with possible rhubarb poisoning. Two cases of apparently healed ulcer are included.

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TWELFTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CHICAGO, ILL., NOV. 5-7, 1942

Round Table Discussion on Reducing the Hazards of the First Two Days of Life

Chairmen: Ethel C. Dunham, M.D., Washington, D. C.
Arthur H. Parmelee, M.D., Chicago, Ill.

Associates: Clara Conrad, R.N., Director of Newborn Nursery, Margaret Hague Memorial Hospital, Jersey City, N. J.
Harry H. Gordon, M.D., New York, N. Y.
James L. Wilson, M.D., Detroit, Mich.
Eleanor I. Leslie, M.D., Chicago, Ill.
Edith L. Potter, M.D., Assistant Professor of Pathology, Department of Obstetrics and Gynecology, University of Chicago Medical School, Chicago, Ill.

Secretaries: Alexander T. Martin, M.D., New York, N. Y.
Roy P. Forbes, M.D., Denver, Colo.
Milo K. Miller, M.D., South Bend, Ind.
Matthew Winters, M.D., Indianapolis, Ind.

CHAIRMAN DUNHAM.—In the brief period since the last annual meeting of the Academy, the problems of public health and medical care have been greatly complicated by the war. The need for increased efforts to protect the health and welfare of expectant mothers and their infants is becoming more and more acute. No one will deny that their preservation is linked inevitably with the future that we are fighting and planning for.

Not only is qualified medical and nursing care becoming increasingly difficult to obtain, but preventive public health services—prenatal, postpartum, and neonatal—are inadequate or entirely lacking in many areas, particularly in defense areas. In addition, a rising birth rate and an increasing demand for hospitalization for delivery, with relatively little increase in hospital beds, have put great strains on facilities for maternity hospital services.

We are here today to confer in regard to steps that should be taken toward reducing the hazards of the neonatal period, particularly the first two days of life. First, I should like to orient you in regard to the vital statistics. It should be pointed out here that we have no nationwide data on causes of morbidity in these periods, and it is indeed unfortunate that we must use mortality rates as the index of accomplishment.

In the past ten years the mortality rate under 1 month of age has shown a definite downward trend (Table I). On the other hand the mortality rate under 1 day of age decreased only slightly during the period 1930-1937 and has tended, in the last three years for which data are available, to become fixed at approximately 14 per 1,000 live births.

In 1940 the total number of deaths on the first day was nearly 33,000 (nearly one-half of the deaths that occurred in the neonatal period) and on the second day, 8,303 deaths, so that approximately 60 per cent of the neonatal deaths occurred before the end of the second day (Table II).

The causes of these deaths in the early neonatal period are shown in Table III. In 1940 63 per cent of all deaths from premature birth occurred under 1 day of age; 56 per cent of those from injury at birth; and 35 per cent of those from congenital malformations.

At this point I want to emphasize the relatively unimportant role of congenital malformations as a cause of death in this period as compared with that in premature birth. In Table IV are shown the percentage of deaths from premature birth and from congenital malformations for four age periods. Among infants under 1 day of age, 60 per cent of the deaths were due to premature birth and only 8 per cent, due to congenital malformations. In contrast, among infants 1 to 3 weeks of age inclusive, only 24 per cent of the deaths were due to premature birth, while 16 per

TABLE I

MORTALITY RATES FOR FIRST DAY AND FIRST MONTH OF LIFE
UNITED STATES EXPANDING BIRTH REGISTRATION AREA, 1930-1940

YEAR	DEATHS PER 1,000 LIVE BIRTHS	
	FIRST MONTH	FIRST DAY
1930	35.7	15.0
1931	34.6	15.0
1932	33.5	15.0
1933	34.0	15.1
1934	34.1	15.4
1935	32.4	15.0
1936	32.6	15.1
1937	31.3	14.7
1938	29.6	14.1
1939	29.3	14.1
1940	28.8	13.9

TABLE II

NEONATAL DEATHS (BY AGE IN DAYS)
UNITED STATES, 1940

AGE AT DEATH	NUMBER OF DEATHS
Under 1 month	67,866
Under 1 week	54,979
Under 1 day	32,870
1 day	8,303
2 days	5,300
3-6 days	8,506
Average per day	2,127
1 week	5,754
Average per day	822
2 weeks	3,777
Average per day	540
3 weeks	3,356
Average per day	479

TABLE III

PERCENTAGE OF DEATHS FROM SPECIFIED CAUSES IN NEONATAL PERIOD
(BY AGE AT DEATH)
UNITED STATES, 1940

CAUSE OF DEATH	AGE AT DEATH		
	UNDER 1 DAY	1 DAY	2 TO 30 DAYS
Premature birth	63	13	24
Congenital malformations	35	11	54
Injury at birth	56	15	29
Other prenatal and natal causes	38	13	49
All other causes	15	7	78

TABLE IV

PERCENTAGE OF DEATHS AT SPECIFIED AGES FROM PREMATURE BIRTH AND CONGENITAL MALFORMATIONS
UNITED STATES, 1940

AGE AT DEATH	PER CENT OF DEATHS FROM	
	PREMATURE BIRTH	CONGENITAL MALFORMATIONS
Under 1 day	60	8
1 day	50	10
2 to 6 days	32	15
1 to 3 weeks	24	16

cent were due to congenital malformations. This is an important finding because it emphasizes the fact that a large proportion of deaths in the early neonatal period are preventable; namely, those due to premature birth.

The problem of reduction of early neonatal deaths is not a new one; but, like most other medical and public health problems, it has been made more acute by war conditions.

The discussions in this round table will be presented in two parts: first, the clinical aspects of conditions associated with hazards to the infant in the early neonatal period, which you have seen has a very high mortality rate as compared with the later neonatal period; and second, the public health aspects of this problem in relation to the war.

Our aim is to discuss specific problems; to present a point of view based on research and experience; and, finally, to make recommendations in regard to steps that might be taken in order to reduce the hazards of the early neonatal period.

Nursing Care of Newborn Infant

Clara Conrad, R.N., Jersey City

I have confined my short discussion on the nursing care of the newborn infant to those fundamental principles, which, if properly interpreted and executed by student, postgraduate and graduate staff nurses, subsidiary workers, and mothers, whether in hospitals or homes, will insure to the baby the greatest chance to survive, and the least danger of morbidity.

The nursing care of the newborn, as we have developed it in the Margaret Hague Maternity Hospital, which, as you may know, has cared for 57,856 babies up to the present time, or since the hospital opened in 1931, has consistently adhered to these basic principles, with, of course, changes in method whenever research indicated revisions. It may also be of interest to you to know that we have an average daily census of 258 newborn infants, an average annual census of 5,500, and that since Jan. 1, 1942, our nursery census has been 6,016. These figures will give you some idea of the need for the carrying out of a simple, safe, and scientific plan.

In the year preceding the opening of the Margaret Hague Maternity Hospital I worked almost daily with Dr. S. A. Cosgrove, our Medical Director and Superintendent, and Dr. J. Phillip Stout, Chief of the Pediatric Service, laying the foundation for the kind of nursery organization and management which would enable us to incorporate successfully the methods and techniques upon which our principles were based.

In 1930 the following fundamentals were considered by us as being the means for safe, simple, and scientific care. They were (1) prevention of infection; (2) prevention of complications due to prolonged or difficult labor; (3) prevention of dehydration; and (4) regulation and maintenance of body temperature.

During the years 1939 to 1941, when Margaret Hague was in the process of rebuilding and while our patients were housed in the Surgical Building of the Jersey City Medical Center, Dr. Cosgrove, Dr. Stout, and I again spent much of our time reviewing our procedures and nursery management. Assuming that the ten years which had intervened had given us a valuable background for analysis and evaluation, we very carefully reviewed statistics on mortality and morbidity, together with our nursery management, and found that even though we were to have new equipment, more space, and perhaps certain environmental advantages, time had proved that the basic principles instituted in 1931 were safe, simple, and scientific and warranted continuance.

I should like, therefore, to restate the governing principles which are applicable universally, if I may be so expansive, and to enumerate briefly our policies and methods for the realization of our objectives.

1. *Prevention of Infection.*—In order to sustain the principle of prevention of infection, we have adopted the following policies and procedures:

1. All personnel, professional and utility, assigned to a nursery are isolated to that area, must have weekly throat cultures, and are immediately taken out at the slightest symptom of a cough, cold, or any skin eruption.
2. Whenever a doctor enters the nursery he is required to wear gown, mask, and cap and must wash his hands thoroughly before proceeding with his work.
3. No visitor is permitted in a mother's room while baby is at breast. Mother is also cautioned about slipping baby under bedclothes, or inspecting baby unnecessarily.
4. At the first evidence of any type of infection, the nurse in charge of the nursery isolates the baby pending the doctor's orders.
5. All nursery linen is washed separately and autoclaved before use.
6. Babies are isolated after rabbinical circumcision.
7. No baby is discharged unless cord is off and umbilicus healed.
8. Babies are fed and changed in their own cribs. The crib is wheeled to the mother's bedside in order to prevent unnecessary handling and exposure.
9. No cleaning, dusting, or sweeping or any other housekeeping activity is permitted during nursing time.
10. No one, including the mother, ever touches the baby without proper hand care immediately before doing so.
11. All bottles and nipples are autoclaved before use. In the home, of course, sterilization by boiling is the accepted procedure.

2. *Prevention of Complications Due to Prolonged or Difficult Labor.*—The following procedures are routine:

1. Baby remains flat for any cerebral condition.
2. Baby remains in Trendelenburg position for mucus.
3. Orders are elastic enough to be changed by the resident or supervisor in charge when, after considering birth history, change in posture is warranted.

4. Tracheal catheter is used for the expression of mucus rather than picking baby up by feet and milking trachea.

5. For hemorrhage, an adequate amount of vitamin K is given, usually ½ to 1 c.c. (intramuscularly) every six hours for four doses. This includes any type of bleeding. It aids in the prevention and treatment of hemorrhage by increasing the prothrombin content of the blood. To replace blood loss the citrate method is used, administration in the cephalic vein.

6. Oxygen can be administered by any nurse to any baby pending the arrival of the doctor.

3. *Prevention of Dehydration.*—In discussing the prevention of dehydration in the newborn, I should like to quote directly from my conversation with Dr. Stout with reference to this particular principle:

"We fussed and stewed for years about loss of weight in babies and have tried every possible fluid. At the present day we do not worry too much about loss of weight unless it is approximately 10 to 12 per cent. Breast feeding is indicated, but the formula is not to be given until the third or fourth day, starting with a weak formula and increasing gradually.

"Two per cent glucose solution is given by mouth, beginning eight hours after birth.

"Clyses of from 0.6 per cent or 0.9 per cent saline solution is given for high temperatures or definite dehydration."

4. *Regulation and Maintenance of Body Temperature.*—The instability of the babies heat-regulating centers requires environmental controls. The nursery is kept at an even 72° F. on the one hand, and the babies body temperature, taken every four hours, indicates the need for increased or diminished covering. When the baby is taken to breast it is wrapped in the carrying blanket, which offsets the change in temperature in the hospital environment. Should the baby's temperature fall below 98° F. rectally, the baby is routinely placed in a heated crib.

Because my time is so limited and my subject so inexhaustible, I feel this is a rather meager attempt to impress you with the importance of what I so courageously said were universal, guiding, and fundamental principles to insure safe, simple, and scientific care of the newborn infant. To offset these discrepancies I have brought with me copies of the results of research on the use of masks, statistics on nursery infections, and copies of a paper which I previously delivered on the Organization and Management of the Obstetrical Department. This paper contains policies and procedures, as well as required equipment for the entire obstetric suite. You are welcome to copies of each. May I add, for myself, Dr. Cosgrove, and Dr. Stout, that should any one of you, at any time, feel the need of either consultation or guidance, please be sure and write to us. In extending this invitation I was assured that if we could not answer the question, we would attempt to solve the problem by whatever type of research or study was indicated.

Plans of the Children's Bureau to Reduce the Hazards of the Early Neonatal Period

Ethel C. Dunham, M.D., Washington, D. C.

I take it for granted that you are all more or less familiar with the various projects for protection of maternity and infancy which the maternal and child health divisions of the various State health departments are engaged in and which are financed in part by funds under the part of the Federal Social Security Act administered by the Children's Bureau. In describing the Bureau's work in this field,

Program for Care of Premature Infants.—The Children's Bureau, in connection with the Social Security maternal and child health program, has encouraged State health departments to develop plans to improve the care of premature infants. Dr.

Bierman and I reported in 1940 that thirty states had presented in their 1940 maternal and child health plan some type of program for their care. Since that time interest in the subject has developed so rapidly that in the plans for 1942, forty-three states presented such a program. It is significant that, in spite of war conditions, the number presenting a 1943 program for care of premature infants is practically unchanged.

The various state maternal and child health plans for the care of premature infants include one or more of the following activities: provision of incubators and emergency kits, postgraduate education of medical and nursing staff in care of premature infants, intrastate institutes for professional and nonprofessional groups, provision of medical and nursing consultants, hospitalization of premature infants, and special studies of hospital facilities and of causes of death of premature infants.

Thirty-two state health departments have provided incubators. The number of incubators so provided (exclusive of those provided by county health departments and those in use in hospitals) exceeds 1,500 according to the answers to a questionnaire sent out in 1942.

Since scientific data on which to base information in regard to incubators were inadequate, the Children's Bureau, in cooperation with the National Bureau of Standards, made a study of electrically heated incubators. As one result of this study specifications for incubators were drawn up which have tended to increase their safety and efficiency. In addition, the Bureau, in cooperation with the National Youth Administration, prepared plans and specifications for three types of incubators: (1) a simple and relatively inexpensive electric incubator, (2) a nonelectric incubator, and (3) a carrier ambulance.

Standards for Care of Newborn Infants.—A major concern of the Children's Bureau has been the setting up of standards for care of newborn infants. In the preparation of these standards, the handicaps due to the present war situation have been given careful consideration, while at the same time emphasis has been placed on the importance of making every effort to maintain the standards of care so essential to the welfare of newborn infants. I feel certain that most of you are being confronted with overcrowded hospital nurseries. You are, I know, well aware of the danger of infection with which overcrowding is fraught.

The necessity for exercising every precaution to prevent outbreaks of infection in hospital nurseries for newborn infants has been repeatedly emphasized in the literature. Sauer and co-workers* reported in April, 1942, that among 942 infants admitted in six years (1923-1928) to a nursery in which aseptic technique was not used, there were fifty-three deaths due to "enteritis." In forty of the fifty-three infants with fatal cases the infection was contracted after admission. During the twelve years since the introduction of aseptic technique, there have been only six deaths due to "enteritis" among 3,132 infants admitted to this same nursery. In no case was the infection contracted after admission.

In spite of increased knowledge in regard to causes of infection of newborn infants and methods of prevention, epidemics still occur. Reports coming to the Children's Bureau indicate that they are increasing along with overcrowding of maternity services. In a number of hospitals (in different cities) epidemics of diarrhea among newborn infants occurring since Jan. 1, 1942, were associated with a high mortality rate, from 30 to 50 per cent.

Newborn infants, both mature and premature, require *special provisions* for care in hospitals:

*Sauer, L. W., Minsk, L. D., and Rosenstern, I.: Control of Cross Infections of the Respiratory Tract. J.A.M.A. 118: 1271-1274, 1942.

1. Medical and nursing personnel in adequate numbers and with adequate training and experience.
2. Atmospheric conditions conducive to their welfare.
3. Sufficient space to permit aseptic, individualized technique of care.
4. Housing of relatively few infants in each nursery unit.
5. Special facilities for premature infants.
6. Provision for isolation of infants who have been exposed to infection or who seem to be developing an infectious condition.
7. A milk room so staffed and equipped as to insure sterile feedings.
8. Apparatus, suitable to the size of infants, always in readiness.
9. Adequate medical and nursing records.

Plans for Hospital Nurseries.—Hospital nursery facilities have been the subject of study by the Children's Bureau. Model plans for nurseries, adaptable to hospitals of various sizes, have been worked out in cooperation with the United States Public Health Service. These plans have been drawn with a view (1) to protecting the infants from infection and (2) to facilitating the work of physicians and nurses. The standards for care already outlined have been used as a guide in developing the plan.

The advantages of such a plan are these:

1. The number of persons entering the nursery is reduced to a minimum; this is, one nurse. An examining room is provided, just outside the nursery, for the use of the physician. Relatives are, of course, not admitted to the nursery, but they may view the infants through a closed window between the nursery and the corridor.

Thus the danger of air contamination is reduced.

2. The bassinets are separated by partitions into cubicles large enough so that bedside care may be given. There is a suspect nursery, completely separated from the nursery proper. Lavatories that have hot and cold running water and faucets with knee or elbow control are conveniently placed in all nurseries and accessory rooms.

Thus the danger of cross infection is further reduced.

3. The nurse's station is so situated that she is in a strategic position to control traffic and to work with a minimum of effort, because (1) the only entrances to the nursery are through her station, (2) windows in partitions make it possible for her to observe the main nursery and the suspect nursery, and (3) the work space is a part of the station. In addition, the bedside tables are stocked with a 24-hour supply of clothing, bedclothes, and diapers, and feedings are delivered to the unit at regular intervals. All this should make it unnecessary for the nurse to leave the nursery in the course of her 8-hour period of duty.

Thus the work of the nurse is greatly facilitated, and her time can be used to the greatest advantage for the care of the infants.

Plans show the setup for hospitals requiring sixteen, twenty-four, and thirty-two bassinets, respectively. Note that as the number of bassinets is increased, the number of nurseries is increased in multiples of eight. The nurses' stations, however, are increased by only one for each two nurseries. A separate nursery for each four premature infants is provided when the number of bassinets exceeds eight. A minimum of two suspect bassinets should be provided, even in the smallest hospitals. Suspect bassinets should be provided in the ratio of one for each five bassinets for well infants. No one suspect nursery should have more than three bassinets.

Medical and Hospital Maternity Care Under the Social Security Act.—As of October, 1942, twenty-nine states have indicated in their maternal and child health plans for the fiscal year 1943, as submitted to the Children's Bureau, that the state health department will finance maternity care for the wives of enlisted men and in

some of these states certain selected groups of other women who cannot pay for such care. In thirteen states this assistance is available to women in any part of the state; in the others it is available in one or more counties. Twenty-one states will pay for prenatal and post-partum care, twenty-one for obstetric consultation; all twenty-nine will pay for hospitalization for delivery. In the state plans for the previous fiscal year, only sixteen states had indicated that the health department would pay for hospital maternity care, and in none of them did this program apply to more than three counties.

It should be pointed out also that as of the same date (October, 1942) Social Security funds amounting to more than $1,500,000 had been requested by these and ten additional states to provide pediatric and obstetric medical care, and hospital care, for the families of men in military service. Thus far only $308,000 has been allocated to meet immediate needs. The allotment of additional funds is dependent on additional appropriations to the Children's Bureau for this important emergency war service.

The importance of this program in the present war emergency is indicated by the fact that the percentage of infants born to wives of men in military service is already substantial and is increasing. Of more than 300,000 infants whose births were registered in May, June, and July, 1942, in twenty-eight states and the District of Columbia, 3 per cent were born to wives of men in the military service. The proportion of married men in the service is increasing—it more than doubled in the 6 months from December, 1941, to April, 1942, and it was conservatively estimated that the proportion of births would reach 5 per cent during the year beginning July, 1942.

Reducing the Hazards of the First Two Days of Life for Premature Infants

Harry H. Gordon, New York

Dr. Dunham has assigned ten minutes for initiation of discussion of the problems of premature infants during the first days of life. In order to conserve time, only certain phases of care will be discussed; it is presumed that the question period will permit elaboration.

Feeding.—There are no quantitative studies of the nutritional requirements of premature infants during the first two days of life, but certain approximations can be deduced from data on slightly older subjects.

Energy: Since the basal metabolism at this time is only from 40 to 50 calories per kilogram per day[1] since activity is minimal and the quotas for fecal loss and specific dynamic action which depend on the food intake are small,[2] it is obvious that the total negative energy balance will be small even if the caloric intake is zero. In other words, the caloric intake during this period need be of no real concern.

Fluid: Maintenance of body fluids is essential but initial stores of body water usually permit some delay in giving fluid. After the first twelve hours the daily administration of approximately 100 to 120 c.c. per kilogram is probably adequate. This recommendation is based on the following findings.

(a) Older premature infants retained adequate water on a total fluid intake of 135 c.c. per kilogram and developed evidence of dehydration when given less than 100 c.c.[3]

(b) The minimal activity and subnormal temperatures of the newborn premature infant are probably accompanied by a smaller evaporative loss of water than was found in older subjects.

(c) Urine flow is not well established in newborn animals and this is probably not solely a question of low fluid intake.[4] Accordingly 100 c.c. per kilogram may be used as a rough average estimate of the need of the premature infant provided there is no vomiting, when it will be greater.

For individual infants, tension of the fontanel, elasticity of the skin, and weight changes should be used in judging hydration of the body. Actually, there are certain pitfalls in their use. Because of mechanical or circulatory factors[5] edema may collect in dependent portions of the body, and this does not preclude the existence of dehydration elsewhere.[6] Raiha[7] has shown that in the first hours after birth the concentration of hemoglobin in the blood increases, a fact which may be explained by passage of fluid from the plasma into the tissue spaces. This may indicate that, under certain conditions, part of the fluid requirements during the first days should be met by the intravenous injection of hypertonic solutions.

In the course of studies of water exchange of premature infants, we have seen evidence of this divergence between weight change and state of hydration (unpublished data). In two premature infants fed boiled human milk and who had loose stools, there was a continued weight gain and large output of urine, although the anterior fontanel was depressed and the elasticity of the skin was diminished. This dehydration may be explained by assumption of a deficit of electrolytes due to loose stools plus low mineral intake (human milk); the weight gain in the presence of dehydration may represent a shift of water from extracellular to intracellular compartments.[6]

The maintenance of acid-base equilibrium in these subjects is closely related to their kidney function. Attention has been called[8] to the tendency of premature infants to develop acidosis.[9] Since young infants have a defect in urea clearance[10] which is probably due to diminished glomerular filtration[11] and since evidence has recently been collected[12] indicating that the ingestion of ammonium chloride is accompanied by a smaller ammonia and greater sodium excretion in premature than in full-term infants, it is probably advisable not to rely wholly on selective renal utilization of sodium chloride solutions for repair of electrolyte disorders in these young infants.[13]

Technique of Feeding: These physiologic considerations of energy, fluid, and electrolyte requirements are only part of the problem. Premature infants have defects in sucking and swallowing and in cough and gag reflexes.[14] This necessitates meticulous attention by specially trained nurses who are given time to perform their duties properly. If gavage is to be used, it must be done expertly. The crude danger of pouring fluid into the trachea is easily prevented; it is sometimes forgotten, however, that reflex attacks of apnea and circulatory collapse can easily be produced by excessive handling. For small infants or infants suspect of cerebral hemorrhage, it may be advisable to forego all oral or gavage feeding, administer fluids, both salt solutions and glucose, parenterally and not worry about caloric requirements.

Vitamins: A word is in order about vitamin requirements during the first few days. Because premature infants are born with low stores of vitamin C[15] and because they frequently have spontaneous hemorrhages, it is probably advisable to give ascorbic acid, particularly to small infants, during the first days of life. No information is available as to the proper dose, but 100 mg. daily for the first two or three days seems a reasonable guess.[15d, 16] This may be given orally or parenterally, depending on the infant's condition.

Since premature infants, like full-term infants, show a neonatal increase in prothrombin clotting time,[17] vitamin K should also be given, preferably parenterally because of their defects in sucking, swallowing, and fat absorption.[18] The exact dose which will produce the desired effects has not been determined. It is our custom at the New York Hospital to give 2 mg. of a synthetic preparation intramuscularly immediately after birth; in infants who are not doing well this dose is repeated after forty-eight or seventy-two hours.

Anoxemia.—In addition to the possible roles of lack of vitamins K and C in the causation of spontaneous hemorrhage, mention should be made of the role of asphyxia

and anoxemia. Ventricular and subarachnoid hemorrhages are frequently found in premature infants with no evidence of gross trauma to blood vessels.[19] Venous stasis associated with asphyxia and direct damage to the capillary walls by anoxemia may contribute to this hemorrhage. Anoxemia may also damage nerve cells directly and contribute to respiratory difficulties.

Dr. Wilson and Dr. Lyon will probably discuss these subjects in detail. We wish only to stress the need for prompt use of oxygen therapy. This requires, first, adequate amounts of nursing care so that infants can be given treatment promptly, and second, facilities for oxygen therapy. Continuous oxygen can be given in some incubators or in a small Burgess tent;[20] intermittent oxygen may be given by mask following meals or other exertion.

Infections.—A few words about the problem of infection. The values of segregation of facilities whenever possible are too obvious to require comment; there is also need for segregation of staff, that is, nurses, and, as far as possible, doctors, who are assigned to the care of premature infants, should not have sick infants as part of their responsibilities. As a further method of diminishing sources of infection, ultraviolet radiation of air and the use of germicidal sprays may prove of importance. Finally, chilling and dehydration[21] should be avoided.

During the past year, our residents, Dr. Samuel Dooley and Dr. Thomas Henley, have prescribed chemotherapy as a prophylactic measure in premature infants with respiratory or other difficulties because of the frequency of secondary infection. There have been no harmful effects, and although there is as yet no proof of its value, its trial has seemed rational. Sulfathiazole or sulfadiazine have been given in divided oral or intravenous doses totaling 0.2 Gm. per kilogram per twenty-four hours. Recently sodium sulfadiazine has been administered subcutaneously[22] in the course of parenteral fluid therapy.

Maintenance of Body Temperature.—The need for supplying extra heat if one is to maintain the body temperature of premature infants is well established. Three particular considerations are worthy of comment. First, if dry heat is used, the relative humidity immediately surrounding the infant will be low. This may produce dehydration of the skin or it may predispose to digestive disorders.[23] Accordingly, incubators which supply additional humidity are preferable sources of heat. Second, to guard against overheating frequent axillary temperatures should be taken, as fever may develop. Day has found that premature infants have a defect in sweating ability, for although they begin to sweat at approximately the same levels of rectal temperature as full-term infants, the perspiration is less in amount.[24] Third, question has recently been raised[25] concerning optimum body temperature for premature infants. Although it would seem wiser on the basis of long-standing clinical impression to try to maintain the rectal temperature of premature infants near 37° F., this level need not be considered a rigid requirement. Of more importance than any arbitrary level is the prevention of wide fluctuations, which directly reflect inadequately controlled environment and inadequate nursing care.[26]

Circulatory Collapse.—Finally, we would like to mention the problem of circulatory collapse. Some premature infants will do well for twelve or twenty-four hours after birth and suddenly go into collapse. In some of these babies, intracranial hemorrhage or sepsis may be present, but in others no cause is found. Clinically, these infants have a cold, mottled skin, subnormal rectal temperature, shallow respirations, and marked muscular hypotonicity. We do not know whether it is fair to call this condition shock in the accustomed sense of the word, but superficially it resembles it. The treatment is unsatisfactory, but as a first measure application of external heat is important. As a second measure, oxygen therapy should be given. Sometimes the

condition occurs after handling, and therefore minimal handling seems indicated. Small doses of 50 per cent glucose, given intravenously, and small transfusions (10 c.c. per kilogram) may be used, but the benefit of such treatment will depend upon the expertness with which it is given. We have given adrenocortical extracts without any obvious benefit. In one infant, the blood sodium was normal during an attack of collapse. Adrenalin is a routine treatment but has seemed of unquestioned benefit only when dire emergency has necessitated its intracardiac administration. This subject of circulatory collapse has been presented because it needs further study.

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Initiation of Respiration in the Newborn Infant

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It is obvious that the best way to save our babies from the danger of anoxia is to prevent respiratory failure in the newborn infant. The most important causes of failure of initiation of respiration or inadequate respiration lie in the brain itself, sluggish in its action, either because of narcosis or trauma. Less important causes lie in the thorax, poorly developed as in the premature, or to too great aspiration of amniotic fluid or other material, each of which, plus a poorly functioning brain, may lead to increased anoxia and incidentally to an abnormal persistence of atelectasis.

To a considerable extent, failure of immediate initiation of effective respiration has been produced by sedation and anesthesia of the mother. The danger of certain drugs in this respect has undoubtedly been exaggerated by some observers and minimized by the obstetricians. I cannot go into this part of the problem except to note that great improvement has already taken place, and that while many obstetricians vehemently deny that they themselves have been at fault, nevertheless, because of the criticism to which they have been submitted, they are becoming much more careful and are using heavy sedation less frequently and more intelligently. I will not take time to discuss brain injury, a big topic in itself, since little can be done for treatment of this condition in the first hour of life, which we are considering.

The practical problems involved in resuscitation of the newborn infant and prevention of asphyxia should not be discussed without some review of the physiology of fetal and newborn respiration. Both the theoretical and practical aspects of this problem are highly controversial, and in discussing it in such a short period it is difficult to avoid being a little dogmatic and expressing personal opinions.

To review some points in the basic physiology: The fetus, at least during the last weeks of fetal life, possesses a blood with a higher hemoglobin content but with a far less total oxygen content than found in normal babies and adults and obviously, therefore, with a far greater per cent of oxygen unsaturation of the hemoglobin. There is also in most cases a much greater difference between the oxygen levels in arterial and in venous fetal blood than is found later in life. Fetal hemoglobin shows an astonishing capacity in carrying and giving up oxygen, which partly explains why the fetus can exist at blood oxygen saturation levels below that compatible with life in older infants. We are still very ignorant about the mechanism of oxygen transport by hemoglobin in the fetus and so far have been unable to study this problem to any extent except by analyses of the blood in the vein and artery of the cord at the time of birth. Data found here, although of great interest, nevertheless cannot possibly supply us with any adequate idea of oxygen consumption or oxygen lack. We know, for instance, that the fetal arterial blood might carry ten volumes per cent of oxygen and the fetal venous blood only two, a difference of eight volumes per cent, while at the same time the mother's blood will show comparable figures of fourteen and twelve, but this in itself cannot teach us much, since, as we so well know, the entire circulation with its system of mixture of arterial and venous blood is quite different in the fetus than in the mother, and we have no way of measuring other important factors such as the volume of blood flow. Studies of oxygen levels in cord blood do not show a very close correlation between anoxia and delayed initiation of respiration.

There have been many attempts to quantitate the degree of anoxia necessary to damage various tissues, but we are still at a loss to measure this properly in the human fetus. It is apparent that the fetal organism, at least in certain small animals, has a tremendously greater capacity to survive anoxia than seen in the adult of that species. Studies done along this line seems to me the most important now

being undertaken in the field of fetal physiology. These observations are just beginning to be followed up, but it begins to be clear that there exists in the fetus of at least some animals a mechanism not present in adults permitting an anaerobic metabolism; that is, a metabolic process that will allow life to persist successfully for some time without oxygen. This protective mechanism in the fetus probably exists in the human being, although we have no good direct proof of it yet, and very likely the fetal brain is much more resistant to damage from anoxia than we have been inclined to think. The total fetal metabolism and, therefore, its need for oxygen, is probably far less than the metabolism of the newborn infant a few minutes after birth. The observations of Barcroft on goats would indicate an increase in total metabolism, that is, of oxygen consumption, of three to five times when the fetus is removed from his marine environment.

The fetal hemoglobin takes up carbon dioxide less readily and gives it up more readily than the maternal hemoglobin; nevertheless a state of comparably severe acidosis exists with a relatively high hydrogen-ion concentration. Carbon dioxide in the blood of the fetus is often not high but other organic acids exist apparently in great excess. It has been taught in the past that failure of respiration is due to a lack of carbon dioxide in fetal blood, but this should not mislead us, since we understand now that the respiratory center is stimulated by a proper hydrogen-ion concentration which exists in abundance in the fetus. Failure of respiration in the fetus represents a failure of a respiratory center depressed by oxygen lack to respond to an existing even greater than normal stimulus, and this fault can be corrected only by getting oxygen to the brain.

The mechanism of respiration is functionally developed long before birth, and more or less coordinated respiratory efforts undoubtedly take place in utero. It is probable that normally very little tidal flow actually results from these respiratory movements, although it is also probable that under certain abnormal circumstances a considerable amount of amniotic fluid is drawn into the lungs. I myself tried to measure the tidal amniotic flow in fetal rabbits with placenta still attached, and making use of a tiny tight-fitting muzzle, I could detect even with vigorous respiratory efforts only as little as one- to two-tenths of a cubic centimeter of actual inspiration of fluid in this submarine respiration. Obviously no observations have been carried out in human beings.

The actual effects of anoxia itself in stimulating intrauterine respiratory efforts is not quite clear. This question is important as it bears on the possibility of anoxia in the fetus, causing vigorous intrauterine respiration and consequent inhalation of large amounts of amniotic fluid. Anoxia has been shown in some small animals to have a very stimulating effect, but Barcroft has shown the effect in various organisms varies with the degree of maturity. It is probable that in the human being at near term a reduction of oxygen supply depresses consistently the respiratory center instead of stimulating it and makes it less sensitive to the stimulus of the hydrogen ion. It is unlikely that the lungs before birth are ever so expanded with abnormal fetal respiratory efforts that the alveoli spaces are distended to anything like the extent that they are often the first few breaths in air.

The actual initiation of the first post-partum breath makes use of a mechanism already existing and to a limited extent functioning. The actual stimulus is quite similar qualitatively, at least from that that makes us continue to breathe for the rest of our life. The first inspiratory effort needs a great deal more physical effort to bring air into the lungs than will be necessary subsequently, and these first very vigorous respiratory efforts must take place at a time when the baby's central nervous system is most apt to be depressed. All babies are born with such air passages as are at all open filled with amniotic fluid, and inspiratory efforts in air inevitably move this fluid further into the lung and spread it throughout the smaller air passages as they become distended. It is apparent that in the vast majority of

instances this cannot be serious, and although no quantitative measurements exist, we can imagine that the amount of fluid filling the trachea and large bronchi at birth when distributed throughout the enormously expanded respiratory surfaces of the baby's lungs after a few successful breaths is spread into such a thin film that it can be quickly absorbed or does not offer serious resistance to the diffusion of gases. However, it is undoubtedly true that in some babies, and it has seemed to some particularly true of those born by cesarean section, that there is a greatly increased amount of fluid in the air passages. Particularly when this fluid is blood and mucus obtained in the passage through the birth canal, aspiration of this material may be a very serious factor in newborn mortality.

The diagnosis of atelectasis is frequently and usually correctly made in babies with poorly developed respiration. One should not think of atelectasis as an explanation of why a baby does not do well but as an inevitable result of poor pulmonary ventilation, whatever the cause. A baby's lung at birth is necessarily atelectatic. How quickly the lung becomes generally expanded will depend upon the vigorous effort and energy of respiration. For a few days a condition of partial atelectasis is normal. Persistence of an extensive atelectasis is usually due to an inefficient respiratory center, but the effects of this may be exaggerated by a poorly developed thoracic cage or by aspiration and consequent greater obstruction of bronchi. I do not think aspiration or excessive fluid is commonly the major cause of persisting atelectasis.

Faced with a baby just born who is not breathing, we are confronted with these practical problems: (1) When should we try to carry out artificial respiration and with what technique? (2) When should we use drug stimulants to respiration? (3) How far should we go in aspirating the respiratory tract to prevent aspiration of the fluid contents held there? (4) With respiration once initiated should we give the baby oxygen or oxygen and carbon dioxide mixtures.

1. If the baby is not breathing, it is obvious that flowing any gas mixture across his nose cannot possibly affect him. This is no time to attempt the nucleus of differential diagnoses as for the reason of the failure of the baby to breathe whether primarily anoxia or whether that is secondary to trauma, intracranial pressure or whether the whole difficulty lies in some gross congenital anomaly. Artificial respiration must be carried out and within a few minutes. The old-fashioned techniques of dunking a baby in hot and cold water and of spanking him, or swinging him around have already been thoroughly laughed at. We should not forget, however, in spite of our present knowledge of certain niceties of the physiology of respiration, that a stimulus to the skin by cold or by a sharp trauma does do something to cause an inspiratory effort. Anyone who has jumped under a cold shower knows this. The point is, however, that such techniques are probably quite ineffective except in babies who are going to breathe with their own efforts anyway and where we do not really need to bother with doing anything. It should be obvious that attempts at manual respiration causing rhythmic pressure on the chest cannot be effective in spite of their traditional use and in spite of the well-known efficiency of the Schaffer method of respiration in people who have breathed. These techniques of artificial respiration all result in first squeezing out air from the lungs and thus reducing their volume to a point below that maintained by the opposing elastic tensions of the thorax and lungs, and then allowing this elastic tension to bring back air into the lungs. This is a mechanism quite upside down from the way we breathe normally, but nevertheless it is as we know quite effective if the lungs have been once distended. This last is not true of the newborn baby. The lungs are collapsed and atelectatic with the walls of the air passages sticking together so that they cannot be further compressed. Necessarily, therefore, attempts at respiration by this technique must be futile. We must therefore come to a decision as to what technique we are going to use to try and produce respiratory efforts, and these will be

either the use of drugs or of one of the following methods: (a) mouth-to-mouth insufflation; (b) the use of positive pressure apparatus of the pulmotor type applied over the mouth; and (c) the Drinker respirator. Although I believe that much better devices for artificial respiration can be devised, nevertheless this is all that we have at the moment. The time to initiate what we have decided to do is obviously a point for an immediate decision. We have to judge how deeply asphyxiated the baby is and how many minutes we can wait for spontaneous breathing to occur. The classic differential between livid and pallid asphyxia, of course, only indicates that there are degrees of anoxia and that the white baby indicates a severe degree to result in contraction of the peripheral capillaries and great slowing of circulation. There is no sharp line between these degrees of anoxia, but we have to learn to recognize that in one we cannot afford to wait as long as in another.

(a) Mouth-to-mouth insufflation is of course the most convenient of all methods of artificial respiration in the infant. I need not point out to you that disrepute into which this method has fallen is brought about by the fact that it is extremely difficult not to use too great pressures, that is, is not uncommon for rupture of the lungs and pneumothorax to occur, and that the danger of infection is very great. However, it still remains a fact that, wanting other instruments, this is a technique that is fairly effective and ready to be used.

(b) Positive pressure machines are growing in popularity. These are devices like the old pulmotor with a fairly tight-fitting mouth- and nosepiece allowing positive pressure to be rhythmically applied over the mouth. Some of the disadvantages of the old pulmotor machine have been avoided. Here again considerable controversy exists as to how effective and how safe these machines are. They are certainly handier to use than the Drinker respirator. They are activated by gas under controlled pressure supplied from standard oxygen or oxygen and carbon dioxide tanks so that they furnish oxygen at the same time. There are certain theoretical objections to their use. Any partially functioning respiratory system opposes by a reflex expiratory effort air blown into the larynx and trachea and probably has an opposite action when suction is applied. The pulmotor type machine by its positive pressure prevents the normal effect of respiration on pulmonary circulation and probably, to some extent, inhibits this circulation.

(c) The Drinker respirator is theoretically a very effective instrument. Practically it seems to me it has been disappointing when used in the newborn infant, and the reasons for this are not wholly clear. One reason, however, is that because of a great fear of causing danger to the lungs it has been used altogether too gently to be effective. Although this fear to some extent is justified, nevertheless it takes a great deal more units of pressure to distend a fetal lung than is generally used with this apparatus. Another objection to the Drinker respirator is the fact that it is awkward to adjust a baby quickly in it and this takes up enough time so that physicians have been loathe to try this until it is probably too late to accomplish much.

The baby's own respiratory efforts, even though quite ineffective, may make those of any mechanical respirator also ineffective, and it seems clear that the efficiency of any mechanical device applying pressure changes rhythmically depends to a great extent on the presence of a relaxed and passive thorax. This objection occurs with both the pulmotor and Drinker respirator. Slight spasm of the glottis can prevent inspiration in spite of a fairly vigorous pressure on the chest as produced by a Drinker respirator.

2. The use of drugs has been widely advocated. Alpha-lobeline and coramine are highly effective, powerful, respiratory stimulants. However, it is apparent that they work on the principle of "beating a tired horse" and that in severe anoxia the

effect upon nerve tissues may be a reversed one and may theoretically destroy any activity still existing in the respiratory centers. It seems to me that these drugs should be used only as a last resort but that their use is then obviously quite justified. I would myself prefer a mechanical method of artificial respiration. Alphalobeline in a dose of 3 mg. given intravenously acts as the best immediate stimulus but its effects are transitory; coramine in a dosage of from 2 to 4 minims given intramuscularly is somewhat better for the maintenance of respiration once initiated. Metrazal, 2 to 3 minims, is preferred by some.

3. What should be done about what has been called the toilet of the upper respiratory tract? There can be no question but that the mouth and throat should be cleaned out by postural drainage and that gentle suction with a catheter is harmless and probably valuable. Suction is certainly not always necessary. Mouth suction with a soft catheter and a sputum trap is quite satisfactory, though most well-equipped hospitals have a mechanical source where the pressure is controlled. The question arises as to whether the procedure should be carried further and a catheter be put through the larynx so that the trachea itself can be aspirated. Certainly this procedure has been enthusiastically advocated by some and has apparently been very successful. Its success will depend, of course, upon the facility with which one can introduce the catheter into the larynx. This is not difficult, especially in a relaxed baby, which is probably the only one in whom it needs to be attempted. Flagg, as you know, has long taught the benefit of direct introduction of a catheter with the aid of a tiny laryngoscope. Positive pressure applied through such a catheter into the trachea is probably much more effective in dilating the lungs than pressure over the nose and mouth, since many of the failures with positive pressure artificial respiration are due, I believe, to the closure of the pharynx either by mucus or spasm.

4. What gas should be used—oxygen or oxygen and carbon dioxide? As I have said in the first place, there is no sense in using either unless the baby is making some respiratory effort or unless in the positive pressure machines these gases induce part of the action of the machine. Whether carbon dioxide is needed in addition to oxygen has long been disputed. It seems to me that all the evidence that has been accumulated in these past years indicates that the real difficulty is due to a depression in the respiratory center due to lack of oxygen and that there exists in abundance and in excess the chemical state in the blood which would powerfully stimulate a normal respiratory center. I very much doubt if there is any effect in giving any additional carbon dioxide and it is quite possible that it is harmful. Pure oxygen theoretically is entirely satisfactory and from my own observations is the gas of choice.

Reducing the Hazards of the First Two Days of Life: The Role of the Rh Factor

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DR. POTTER.—The Rh factor, discovered by Landsteiner and Wiener in 1940 and first postulated as an etiologic agent in the production of erythroblastosis by Levine and his associates in 1941, is arousing constantly growing interest. Knowledge concerning the probable cause of erythroblastosis has been lacking until the present time, although it has been recognized as a clinical and pathologic entity for many years.

Erythroblastosis is a disease in which the primary disturbances consist of an excessive destruction and an abnormal production of red blood cells. These conditions are ordinarily associated with abnormal accumulation of fluid in the skin, subcutaneous tissues and body cavities, or with marked icterus. Occasionally both edema and jaundice are present and occasionally both are absent.

It should be stressed that the terms fetal hydrops and icterus gravis are not synonymous with erythroblastosis. Jaundice may occur in septicemia, syphilis,

unexplained liver degeneration, and other conditions, and severe fetal hydrops is often entirely unassociated with erythroblastosis. I have observed seventeen infants at autopsy (being reported elsewhere) with ansarca and pleural and peritoneal effusions in whom the cause was not erythroblastosis. (During this same period erythroblastosis has been found in fifty infants.)

In order to establish the clinical diagnosis of erythroblastosis anemia, erythroblastemia, and splenomegaly must be present; if the patient succumbs, autopsy examination must show erythropoiesis in areas where red blood cells are never normally produced. Any one of these individual findings may occur in other conditions, but except in rare cases of syphilis and septicemia, the combination of all four is found only in erythroblastosis. Other manifestations which are usually associated are edema or jaundice, hepatomegaly, pigmentation of hepatic cells, absence of Malpighian corpuscles in the spleen, increased icterus index, placental hypertrophy. Less constant are pigmentation of nerve cells in the brain, tubule cells in the kidney, and macrophages in spleen and liver; bile thrombi in the liver; hypoplasia of the thymus, mild hypertrophy of the heart; hyperplasia and hypertrophy of the Islands of Langerhans; excessive numbers of hemacytoblasts in the capillaries of the lungs; maternal polyhydramnios. Erythropoiesis is always most marked in the liver, spleen, and kidneys, but it may be found in the connective tissue located in any organ or any part of the body.

The reason for stressing the diagnostic features of erythroblastosis lies in the fact that at the present time, the diagnosis is being made too widely and on insufficient evidence by those having some knowledge of the disease, and on the other hand, is still being overlooked in many instances because the physician is unaware of the existence of such a condition.

The Rh factor as far as the hazards of the first two days of life are concerned is important only in its possible relation to the production of this disease.

The Rh factor is a term applied to an antigenic substance which bears no relation to previously known blood groups and which is normally present in the blood of 86 to 88 per cent of all human beings, male and female alike. Those individuals whose blood contains the Rh factor are considered Rh+; those in whom it is absent are Rh–. This is determined by the test tube response of blood cells to sera known to contain anti Rh agglutinins. If Rh+ cells are introduced into the blood of a person who is Rh–, anti Rh agglutinins may be produced in the body of the Rh– individual. The Rh factor is inherited as a Mendelian dominant, and when an Rh– woman bears children by an Rh+ man, 50 per cent of the offspring will be Rh+ if the Rh factor is heterozygous in the man; 100 per cent will be Rh+ if it is homozygous.

The theory proposed by Levine and co-workers postulates that, given an Rh– woman and an Rh+ fetus, a break in the fetal circulation within the placenta will permit the entrance of Rh+ fetal cells into the Rh– maternal blood. Anti-Rh agglutinins may be produced by the mother and these in turn may pass from the maternal blood through the walls of the villi and enter the fetal circulation. The adverse effect of the agglutinins on the fetal hematopoietic system may result in the production of erythroblastosis.

In approximately 12 per cent of all marriages the wife is Rh–, the husband Rh+, but erythroblastosis actually occurs in only 0.1 to 0.2 of all pregnancies. The reason for the discrepancy between the actual incidence and the possible number which could occur can be explained by the many variables which exist. As far as is known a break in the fetal circulation rarely occurs, and this is probably the great limiting factor in the production of the disease. The variability (1) in the antigenic potency of the Rh factor, (2) of the ability of the maternal organism to produce antibodies, (3) of the transmissability of the antibodies through the walls of the villi, and (4) the manner in which fetal tissues respond to the presence of antibodies are all modifying elements. Limitation in the number of offspring also de-

creases the incidence; if every married woman were to have six or eight children, the increase in erythroblastosis would be proportionately much greater than would be expected on the basis of the increased birth rate.

I have observed two other conditions which may be related to the production of erythroblastosis although a definite correlation has not yet been established. These are (1) a disproportionately large number of males among offspring born prior to the occurrence of erythroblastosis, with the last preceding infant almost invariably being male, and (2) an individual or family history of hay fever, asthma, and other allergic manifestations.

The basic conditions (Rh- mother, Rh+ father, Rh+ fetus) necessary for the production of erythroblastosis according to this theory have been shown to exist in a very large proportion of the cases which have been investigated. Levine, Burnham, Katzin, and Vogel found 93 per cent Rh- in a group of 153 women giving birth to infants with erythroblastosis, and Potter, Davidsohn, and Crunden found 90 per cent Rh- in a group of sixty similar women. The Rh factor is not a specific uniform entity but appears to be rather a mosaic of interrelated antigenic substances. All cells do not react uniformly with all sera containing known anti-Rh agglutinins, nor are the results obtained using human sera always in agreement with those obtained using sera from rabbits produced according to Landsteiner's original method. For this reason multiple testing is desirable.

It may be possible that the 10 per cent who are Rh+ might be shown to be Rh negative if a wide enough variety of testing sera were available; in other words, if a woman lacks any fraction of the Rh substance, and this particular fraction is present in fetal cells, immunization against it may be produced.

Another reason for the existence of 10 per cent who are Rh+ may be that the diagnosis is in error in those cases. In my experience no case which has been entirely typical has been found associated with Rh+ maternal blood. Although 10 per cent of those mothers who have been tested, on whose infants I have made a diagnosis of erythroblastosis, have been Rh+, all of these infants have had some atypical feature, and it is possible the diagnosis was not warranted. It would seem that with an Rh+ mother, the diagnosis of erythroblastosis is open to grave question.

The practical application of knowledge concerning the Rh factor is extremely limited in so far as it may decrease the hazards of the first days of an infant's life. It would be of interest to make Rh determinations on all prospective parents, but since erythroblastosis at present is found in only about 2 per cent of those marriages where the wife is Rh- and the husband Rh+, it is not advisable to limit either marriage or the bearing of children because of this. The diagnosis of erythroblastosis can be made only by examination of the affected infant, and although knowing that the mother is Rh negative may aid in corroboration of the diagnosis, it does not, in itself, establish the diagnosis.

If a woman once gives birth to an infant with erythroblastosis, the prognosis for future normal pregnancies is very poor; in the great majority of cases, all subsequent infants are affected by the same disease. It has been suggested that during any pregnancy following one in which the fetus was affected by erythroblastosis, the mother's blood be tested at frequent intervals for the presence of anti-Rh agglutinins. If they suddenly appear when previously absent, or if the titer increases, it has been advocated that cesarean section be performed immediately in hope of delivering a fetus who has not been too profoundly affected by the anti-Rh agglutinins. This also is not practicable, for only a small percentage of women show demonstrable agglutinins at any time, and in many instances the fetus is already affected before it has reached the stage of viability. To perform a cesarean section in order to deliver an infant prior to term in hope that it will escape being affected may, in our present state of knowledge, seem justifiable, but in the great majority of instances

the outcome is no different than it would have been had nature been permitted to take its course.

The treatment of any infant with erythroblastosis is immediate transfusion. The anemia is often so profound that the red cells are insufficient in number to accomplish tissue oxygenation, and the number must be increased if the infant is to survive. Blood for transfusion should, if possible, be Rh- on the possibility that anti-Rh agglutinins are circulating in the fetal blood and should in no case come from the mother, whose agglutinins are believed to have been the cause of the disease. If known Rh- blood is not available, careful crossmatching at 37° C. for thirty minutes will ordinarily suffice.

A tentative diagnosis of erythroblastosis may be made prior to delivery if it is known that a previous pregnancy has resulted in the birth of an affected child. In such cases facilities should be ready at the time of delivery for immediate transfusion, intubation, or tracheotomy, removal of intrathoracic fluid, administration of oxygen, etc. Vitamin K is rarely needed as few of these infants have a prolonged prothrombin time. Iron and liver preparations are too slow in their action to be of benefit. No treatment of the mother prior to or during pregnancy has yet been found which will prevent erythroblastosis from developing.

Summary.—The discovery of the Rh factor and the seeming establishment of its relation to the etiology of erythroblastosis has given new impetus to the study of this disease. Although knowledge concerning the Rh reaction of mother, father, or infant is of little or no practical importance in the diagnosis, prevention, or treatment of the disease, as many individuals as possible should be tested in order that further knowledge may be accumulated. If the mother is Rh+, a diagnosis of erythroblastosis should be made with caution, and only on the most complete evidence. It should also be remembered that only about one in sixty women who are Rh- will give birth to babies with erythroblastosis.

Birth Injury

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Injury at birth ranks second to prematurity as a cause of death in the first month of life. In 1939 it was responsible for 9,955 deaths of newborn infants in the United States, or 15 per cent of the total number of deaths of that age period (4.4 per 1,000 live births). The diagnosis of birth injury is frequently difficult to make, but it is probable that many of the above deaths were due to hemorrhage into some vital organ, notably the brain.

Two factors make hemorrhage a dangerous condition in the neonatal period. One is the mechanical rupture of blood vessels which seems to occur frequently from the trauma of birth, and the other is the delay in the clotting of blood, a condition which has been termed the hemorrhagic tendency of the newborn infant. There is general agreement now that the hemorrhagic disease is due to an absence, or the failure of activation, of prothrombin. Prothrombin is a pseudoglobulin occurring in the blood plasma and probably stored in the liver. Together with calcium and thromboplastin, it forms thrombin which is converted by action with fibrinogen into fibrin.

During the first days of life the prothrombin content of the infant's blood often sinks to dangerous levels but rises spontaneously thereafter until by the end of the first week of life it has been restored to normal amounts. If no blood vessel damage occurs, the infant escapes serious symptoms. The mechanism by which the infant restores his supplies of prothrombin is not known, but it is probably from the injestion, or the synthesis of the activating vitamin K in the intestinal tract.

With the advent of vitamin K, a specific therapeutic agent became available. This vitamin, discovered by Dam in 1934, was derived from alfalfa, leafy vegetables, bacterial cultures and from several body tissues, and other sources. Within a sur-

prisingly short time, the chemical nature of the vitamin became known, and the most commonly used products today are synthetic naphthoquinones which are very effective drugs causing a rapid rise in the prothrombin levels in the blood of newborn infants who have depleted stores. When given immediately after birth or when given to mothers before the infants are born, they prevent the customary drop in prothrombin.

Many favorable reports have been made on the results of vitamin K therapy. In many instances the success of its administration has been judged from the response of the prothrombin level in the first week of life, but there have also been clinical observations of note. The most dramatic results occur in the infants who have some bleeding from an external source such as the umbilicus, which is checked within an hour or two after the administration of vitamin K. The incidence of retinal hemorrhages has been lower in newborn infants whose mothers received the vitamin than in untreated control groups of patients. Finally, intracranial hemorrhage has seemed to be less frequent than average in infants whose mothers had received the vitamin during labor. Some of the clinical manifestations of hemorrhage occur so infrequently that long experience must be awaited to be certain of the effect of the vitamin therapy.

Our own experience has been limited. We have been inclined to divide hemorrhage of the newborn infant into three categories in respect to its clinical manifestations. The first is persistent hemorrhage from visible bleeding points such as the nose and umbilicus and including also the occurrence of gross blood in vomitus or stools. Among a group of about 8,000 liveborn infants such symptoms occurred in 7 per thousand before the advent of vitamin K. Since the vitamin has been given routinely to all mothers, the incidence of this symptom has dropped to 3.05 per thousand live births in a group of about 1,000 infants. The infants in these two groups were not observed simultaneously. The second type of hemorrhage is a self-limited variety, closely related to birth trauma, and appears as ecchymoses in the skin, conjunctival hemorrhages, and cephalohematomas. Vitamin K therapy has not influenced the incidence of these manifestations in our brief experience. The third type of hemorrhage is internal bleeding, especially intracranial. Here the diagnosis is more difficult, and only about one-half of our patients suspected of having this condition have come to autopsy and the remainder have been diagnosed from clinical symptoms and from the finding of blood in the cerebrospinal fluid. Since the administration of vitamin K, the incidence of intracranial hemorrhage has dropped from 9.8 to 7.1 per thousand live births. Hemorrhage into other vital organs such as the liver, adrenal glands, and lungs has not been affected by the vitamin administration, but these are such rare manifestations that one such case can greatly influence percentages unless a large number of patients have been under observation.

Studies from other clinics have recorded better results than ours in respect to intracranial hemorrhage. It would be safe to conclude at this time that the routine administration of vitamin K is a highly effective means of reducing the prolonged bleeding of the newborn infant but that it cannot be expected to prevent entirely the damage caused by traumatic injury to blood vessels.

The vitamin may be administered to the infant immediately after birth by mouth, by intramuscular or intravenous injection, or even by rubbing it into the skin. Better, however, is its administration to the mother during labor. The preparations available are divided into two general categories; the natural vitamin which is usually given by mouth to the mother at least from four to six hours before the delivery of her infant. When given to the infant after birth, about two hours are required for its action to take effect. The synthetic vitamin may be given by any route but when injected intravenously, it produces the most rapid response. It should be given to the mother at least two hours before delivery and not earlier

than about twelve to fifteen hours before. When administered to the infant intravenously, the effect may be noticed within the next hour.

Blood transfusion, which was once the sole effective method of treatment of hemorrhagic disease of the newborn infant, is still a valuable aid in treating such infants if there has been a significant loss of blood.

Organization for the Care of Infants in the Connecticut State Defense Program

In Connecticut there is a Pediatric Advisory Committee to the Medical Representative on the State Defense Council. This committee has no authority but gives its advice on all matters pertaining to the evacuation of infants and children in defense areas. Shortly after Pearl Harbor the committee, confronted with numerous miscellaneous problems, decided to develop a comprehensive practical program that could be put into effect if and when the need arose. Every pediatrician in the State of Connecticut was appointed on some subcommittee organized to consider a particular phase of the general program, such as care of children with communicable diseases, healthy preschool children, children with mental difficulties, etc. There were twelve subcommittees. Their reports have been submitted to and edited by the Pediatric Advisory Committee and will within a few days be off the press. (Copies can be obtained from the Bureau of Child Welfare, State Office Building; or State Defense Council, State Armory, Hartford. For nonresidents of Connecticut the cost is 25 cents.)

The subcommittee on the Care of the Newborn, as did the other committees, considered its problem in relation to (1) bombing, (2) short-term evacuation, and (3) long-term evacuation. Naturally, in the care of the newborn infant, the pediatrician's problems are closely related to the program adopted by the obstetricians and must include the consideration of babies born (1) in hospitals, (2) at home, (3) en route, and (4) in reception areas.

We have already seen one effect of the war on newborn infants. Our hospitals are so crowded that we have had to send mothers and babies home on the seventh or eighth day instead of the fourteenth as formerly, but we have seen very few bad effects from this curtailed stay in the hospitals.

Only if and when the authorities decide to evacuate hospitals will our program concerning newborn infants be put into full effect, but preliminary surveys have been and are being made. The first rule is that a mother and her baby should be kept together if at all possible. The second rule is that only the most meager equipment consistent with safety can be taken along. As the institutions or homes in the reception areas will vary in size, we have drawn up our plans on the basis of units of ten babies. We have considered such things among the three dozen articles needed, as the number of diapers, blankets, bottles, nipples, sterilizing equipment, and medication.

If the babies born at home have to be evacuated, the mothers will be advised on necessary equipment such as identification tags, clothing, and feeding utensils. Also, there is a list of articles which would be handy but which, in case of necessity, can be provided in reception areas—evaporated milk, corn syrup, sterilizing kettles, etc.

If babies are evacuated to large institutions in reception areas, we hope to provide a skeleton staff of pediatricians and pediatric trained nurses, but if babies are sent to individual homes or small units in reception areas, we consider the advisability of mobile ambulances equipped with oxygen, emergency drugs, foods, means for administering subcutaneous salines, etc. Most of the routine care will be left to public health nurses.

We have devised a somewhat similar plan for premature babies, including a detailed list of necessary equipment. For the transportation of premature infants, we have adopted the unit devised by the Alabama State Department of Health.

DISCUSSION

DR. L. M. EARLE, HOLLYWOOD, CALIF.—Do you use a tracheal catheter and who uses it?

DR. GORDON.—Yes, it is done by the resident in the delivery room.

DR. K. M. BUCK, MEMPHIS.—Is your personnel trained in bronchoscopy?

DR. WILSON.—Drainage and suction may be necessary. The proper equipment must be present at all times and if the baby does not breathe properly he should be resuscitated.

DR. C. R. BROWN, ARLINGTON, N. J.—I feel someone who is properly trained must be designated and held responsible if resuscitation is necessary.

DR. WILSON.—You do not have to resuscitate the moment baby is born. Resuscitation may be attempted by the following methods: Mouth-to-mouth breathing, Drinker respirator, or by pulmotor. The Drinker method is not too acceptable. I do not recommend placing the baby in hot and cold water.

DR. B. M. BEACH, NEW ORLEANS.—Dr. Gordon, what have you to say regarding the use of sulfonamides?

DR. GORDON.—They are well tolerated in almost all infants. They may be given orally or intravenously. I have seen very few harmful effects in their use, such as hematuria or sensitization. In two premature infants erythema nodosum was noted.

DR. M. M. NICHOLSON, WASHINGTON, D. C.—Has the pancreas been examined in babies who died following the use of sulfonamides?

DR. GORDON.—No.

DR. A. P. BLOXSOM, HOUSTON, TEXAS.—The delivery room must be a recovery room. The newborn infant should not be sent two or three floors below to receive necessary treatment.

DR. GORDON.—This is very important. There must be a close coordination between the obstetric and pediatric departments.

MISS CONRAD.—Do you give iron and ascorbic acid?

DR. GORDON.—I do not give iron routinely in newborn infants. Give a transfusion if necessary. Ascorbic acid is given at the end of the first week.

DR. GORDON.—What about transfusion the first few days of life to prevent hemorrhage?

DR. LYON.—Transfusions are not really necessary; the administration of vitamin K will suffice.

DR. GORDON.—Do you recommend spinal puncture in the newborn infant?

DR. LYON.—Yes, sometimes we do "taps" in the hope we will gain some information. We are seldom benefited by our efforts.

CHAIRMAN DUNHAM.—What amount of blood do you use in transfusing premature infants?

DR. GORDON.—Give small amounts, 10 c.c. per kilogram. It can be given with a syringe without much handling. It may be given in the scalp, wrist, or ankle vein.

DR. F. HALL, NEW ROCHELLE, N. Y.—Is it necessary to have typing done?

DR. POTTER.—For all practical purposes, typing is not necessary. Agglutination tests are sufficient. The mother should not be used; use a donor from outside the family group. If possible, get a negative Rh donor.

DR. A. S. BROWN, WATERBURY, CONN.—When does the mother lose antibodies?

DR. POTTER.—Many show no antibodies; this is very interesting. All severe icterus and hydrops are not erythroblastosis. We must be careful about the diagnosis.

DR. M. K. WYLDER, ALBUQUERQUE, N. M.—After a mother gives birth to an infant with erythroblastosis, can anything be done?

DR. POTTER.—Get rid of the husband.

DR. BENJAMIN HOYER, CINCINNATI.—What is the value of the use of ultraviolet lights in the nursery?

CHAIRMAN DUNHAM.—Enough reports have been published to benefit their value, for use probably cuts down the instances of infection.

DR. WILSON.—There is a definite reduction in bacterial count. I would advise waiting until the true value of the use of propylene glycol is shown before installing the ultra violet lights.

DR. W. E. WHEELER, DETROIT.—Is it necessary to control the humidity of the nursery?

DR. WILSON.—Full-term babies do not need high humidity.

DR. WHEELER.—Our experience has been that with the use of humidity control, there has been a marked decrease in dehydration and weight loss in our regular nursery.

DR. WHEELER.—What about anoxemia in the newborn infant?

DR. WILSON.—Put in an oxygen tent. Use a plastic cone using two liters of oxygen per minute. Give the youngster in the tent from forty-eight to seventy-two hours.

DR. WHEELER.—What about the use of gauze masks?

MISS CONRAD.—Our experience showed that cross infection was less without masks than with them. But all the personnel in the nursery here is required to have a throat culture taken once a week. Those showing a positive culture hemolytic streptococci were eliminated from the nursery. Dr. May of Detroit condemned the use of lowering the baby's head after birth. This increases the blood supply to the brain and might increase hemorrhage if there is a tendency to bleed. Dr. May also condemned the use of gauze on the doctor's finger in cleansing the infant's mouth.

The question of resuscitation of the newborn infant was discussed by Dr. Wilson. The question of the necessity of routine aspiration of the trachea was also discussed. Mouth-to-mouth resuscitation might be dangerous but at times is necessary. The use of an artificial respirator is of no value if the larynx is closed. The use of the Drinker respirator has been very disappointing. It certainly is not good if the larynx is closed. The use of drugs such as alpha-lobeline and coramine may be effective but usually are disappointing.

Dr. Clement Smith, of Boston, described an effective method of using oxygen in the baby's basket based on the fact that oxygen is heavier than air. It, therefore, sinks to the lower part of the basket.

The Pediatrician and the War

Emergency Maternal and Infant Care

Reference was made to the program of Emergency Maternal and Infant Care in the June issue of the JOURNAL on page 736. In the June Appropriation Act, approved July 12, 1943, Congress appropriated $4,400,000 in the form of grants to States for this work.

In the same Act a proviso was written in that no part of the appropriation could be used to promulgate or carry out any instruction or order or regulation relating to the care of obstetric cases which discriminated between persons licensed under State laws to practice obstetrics, and further that this should not be so construed as to prevent any patient having the services of any practitioner of her own choice, and paid for out of this Fund so long as the State laws are complied with.

The above provision prohibits the Children's Bureau from establishing minimum qualifications for practitioners as a condition of State approval as far as obstetric services are concerned. As a result it automatically follows that such conditions as were previously outlined by the Bureau are revoked. Pediatrics was not mentioned specifically as was obstetrics in the Law.

News and Notes

The National Association for Nursery Education is holding its Tenth Biennial Meeting in Boston, Mass., Oct. 22 to 25, with headquarters at the Hotel Statler. This will be a work study conference on "The Community Serves the Child in War and Peace." Registration opens the morning of October 22, and the first general session will be that evening on the topic "The World Picture and the Implications for Education." The subsequent sessions will consist of study groups which will discuss child development problems based on actual case histories of various communities. Special features will include curbstone meetings, educational exhibits, and a public relations booth. The problems of young children, intensified by present war conditions, can only be solved by persons interested in protecting and improving health, welfare, and education. Despite travel curtailment it is hoped that, because of the vital need for coordinated planning and action, as many leaders in the field as possible will make an effort to participate.

Attention is directed to certain wordings in the Report of the Committee on Therapeutic Procedures for Acute Infectious Diseases and on Biologicals of the American Academy of Pediatrics, revised October, 1942. On page 38, under XLII. YELLOW FEVER, A. Tests: the sentence, "Castaneda modification of Weil-Felix agglutinin test of blood serum against *B. Proteus* X19: 1:100 titer will give a weak positive reaction when bedside cards are used," should be placed on page 36, under XXXIX. TYPHUS, A. Tests. The word, "None," should be transferred from XXXIX. TYPHUS, A. Tests to appear under YELLOW FEVER, A. Tests: before the sentence, "Virus can be isolated from the blood stream."

The Committee on Therapeutic Procedures for Acute Infectious Diseases and on Biologicals of the American Academy of Pediatrics wishes to issue the following note on penicillin:

> "Penicillin is being made in increasing amounts, yet it is not available for general distribution at the present time. Indications following its use in specially selected hospitals, medical schools, and the armed forces point to an effectiveness greatly superior to that of the sulfonamides. Experience thus far has demonstrated the drug to be effective against the "*Staphylococcus aureus*, the pneumococcus, meningococcus, *Streptococcus pyogenes*, and *Hemolytic streptococcus*. The drug is particularly valuable in wounds. It is believed that when osteomyelitis is treated early it will no longer be necessary to resort to surgery for its cure. The minimum effective dose for man is apparently not yet determined. The drug is devoid of toxic reactions in usual doses. The synthetic preparation of penicillin due to its complex chemical nature seems remote."

The following dates have been set for examinations to be given to candidates by the American Board of Pediatrics:

Written examination, locally under a monitor, Feb. 4, 1944.

Oral examination, Philadelphia, Pa., March 25 and 26, 1944, San Francisco, Calif., May 6 and 7, 1944.

Book Reviews

Convulsive Seizures. Tracy J. Putnam, M.D., Philadelphia, 1943, J. B. Lippincott Co., 168 pages. Price, $2.

This manual is written primarily for patients with convulsive disorders in order to give them sound and easily understood information about the nature and treatment of their difficulties. It is intended further to give them and the general public some idea about the improved prognosis which has resulted from scientific study and to stimulate public interest so that there may be a change of the conventional attitude toward convulsions, improvement in facilities for the care of patients, and new consideration to legal aspects of the situation. The pediatrician will find the book valuable as a short review of the causes and the types of common convulsive seizures and as a practical guide in their diagnosis and treatment. Descriptions of the new diagnostic aid, the electroencephalogram, and of the new anticonvulsant drugs are presented clearly and without undue technical detail. The inclusion of some discussion about psychologic management as a necessary part of the medical and surgical treatment is heartening and should aid the modern pediatrician to overcome the dichotomy of mind and body which still persists in so much of our medical management of the sick person. Several pages on the hereditary and socio-economic aspects will provide the physician with good background material for answering the patients' questions about marriage and childbearing. Finally there is a brief review of the legal and legislative aspects as related to the employment, legal responsibility, and sterilization of individuals having convulsive seizures.

SENN

The Boy Sex Offender and His Later Career. Lewis J. Doshay, M.D., Ph.D.; Foreward by George W. Henry, M.D., New York, 1943, Grune and Stratton, 248 pages. Price, $3.50.

This is an inquiry into the significance of early sex offenses by male children in relation to their later life behavior. It is a study made by analyzing the early traits and adult outcomes of two groups of boys, comprising 256 cases of juvenile sex delinquency and treated in the New York City Court clinics between 1928 and 1934. The individuals observed were divided into a "primary" group having no known involvement of any other offensive behavior other than sexual, and a second group who had engaged in a "mixed" set of offenses. By detailed statistical analyses the "primary" has been compared with the "mixed" group as a control.

Results of the survey point out what unfavorable home, economic, and health conditions foster the development of deviant behavior and demonstrate those determining factors in the background, personality, and behavior of the delinquents that relate to success or failure in adult life. Criteria for the prevention and treatment of similar cases are outlined.

The book is a good one for reference by those pediatricians working as school physicians or as members of a unit engaged in psychiatric, child guidance, and court work. The detailed analyses and case studies which make up the study will be of value, as will be the detailed bibliography relative to delinquency generally. For the pediatrician in the usual practice with children and adolescents, this book will provide information on a topic with which the average pediatrician is unfamiliar because of his infrequent contact with the child having an extremely deviant personality; and by this token, it will be of limited or sporadic usefulness to him. The brief sections on physical status of the boy sex offender and its prevention provide material which every physician should know about and which should be imparted to the pediatrician-in-training as part of his education in pediatric psychiatry. The excellent results of the clinic therapy are pleasantly surprising, but the conclusion of the author that guilt and shame stimulated by court attendance are the active principles must be accepted with reservation. This book should certainly be a part of the library of every pediatric teaching center, although not necessarily of every individual practitioner. SENN

Clinical Significance of the Blood in Tuberculosis. Gulli Lindh Muller, M.D., New York, 1943, The Commonwealth Fund, 516 pages. Price, $3.50.

The contents of the book is divided into six major parts as follows: physiology of the blood-forming organs and cellular response to the tubercle bacillus; changes in the circulating blood in tuberculosis; the sedimentation rate; clinical and hematological data as measures of constitutional reaction; the effect of therapeutic methods, exercise, and certain complications of the hematological picture; examination of the blood. The material from the author's own work is finely analyzed and discussed. Conclusions are presented after each chapter so that the findings are properly correlated with the available information from other sources.

The book is really a careful study of the blood from a general standpoint, and a great deal of the material would be useful in conditions other than tuberculosis; rheumatic fever, for instance. Besides it should serve as an important reference for any one interested in tuberculosis seeking information in this limited field. It is interesting to find that so much can be done by painstaking study of a subject which one might assume these days is threadworn. The book can be recommended for those interested in the subject. The publishers have, as usual, done a good job of editing and printing. The general effect is so pleasing that one does not miss the expected, and probably superfluous, color plates of stained blood cells usually found in books on hematology. MCCULLOCH